

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/06	A1	(11) International Publication Number: WO 95/05192 (43) International Publication Date: 23 February 1995 (23.02.95)
<p>(21) International Application Number: PCT/US94/08868</p> <p>(22) International Filing Date: 8 August 1994 (08.08.94)</p> <p>(30) Priority Data: 106,468 13 August 1993 (13.08.93) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 106,468 (CIP) Filed on 13 August 1993 (13.08.93)</p> <p>(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HAGMANN, William, K. [US/US]; 871 Shackamaxon Drive, Westfield, NJ 07090 (US). MJALLI, Adnan, M. [JO/US]; 285 Elm Avenue, Rahway, NJ 07065 (US). ZHAO, Justin, J. [CN/US]; 1586 Irving Street, Rahway, NJ 07065 (US). MacCOSS, Malcolm [GB/US]; 48 Rose Court, Freehold, NJ 07728 (US).</p>		<p>(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FL, GE, HU, JP, KG, KR, KZ, LK, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).</p> <p>Published With international search report.</p>
<p>(54) Title: SUBSTITUTED KETONE DERIVATIVES AS INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME</p> <div style="text-align: center; margin: 20px 0;"> <p style="text-align: right;">(I)</p> </div> <p>(57) Abstract</p> <p>This invention relates to substituted ketone derivatives of formula (I) useful in the treatment of inflammation in lung, central nervous system, kidney, joints, endocardium, pericardium, eyes, ears, skin, gastrointestinal tract and urogenital system. More particularly, this invention relates to substituted ketone derivatives that are useful inhibitors of interleukin-1β converting enzyme (ICE). Interleukin-1β converting enzyme (ICE) has been identified as the enzyme responsible for converting precursor interleukin-1β (IL-1β) to biologically active IL-1β.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

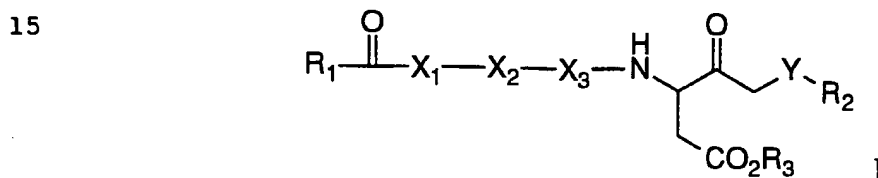
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

TITLE OF THE INVENTIONSUBSTITUTED KETONE DERIVATIVES AS INHIBITORS OF
INTERLEUKIN-1 β CONVERTING ENZYME5 BACKGROUND OF THE INVENTION

This invention relates to substituted ketone derivatives of
Formula I useful in the treatment of inflammation in lung, central nervous
system, kidney, joints, endocardium, pericardium, eyes, ears, skin, gastro-
intestinal tract and urogenital system. More particularly, this invention
10 relates to substituted ketone derivatives that are useful inhibitors of
interleukin-1 β converting enzyme (ICE). Interleukin-1 β converting
enzyme (ICE) has been identified as the enzyme responsible for
converting precursor interleukin-1 β (IL-1 β) to biologically active IL-1 β .



20 Mammalian interleukin-1 (IL-1) is an immunoregulatory
protein secreted by cell types as part of the inflammatory response. The
primary cell type responsible for IL-1 production is the peripheral blood
mono-cyte. Other cell types have also been described as releasing or
containing IL-1 or IL-1 like molecules. These include epithelial cells
25 (Luger, *et al.*, J. Immunol. 127: 1493-1498 (1981), Le *et al.*, J. Immunol.
138: 2520-2526 (1987) and Lovett and Larsen, J. Clin. Invest. 82: 115-
122 (1988), connective tissue cells (Ollivierre *et al.*, Biochem. Biophys.
Res. Comm. 141: 904-911 (1986), Le *et al.*, J. Immunol. 138: 2520-2526
(1987), cells of neuronal origin (Giulian *et al.*, J. Esp. Med. 164: 594-604
30 (1986) and leukocytes (Pistoia *et al.*, J. Immunol. 136: 1688-1692 (1986),
Acres *et al.*, Mol. Immuno. 24: 479-485 (1987), Acres *et al.*, J. Immunol.
138: 2132-2136 (1987) and Lindenmann *et al.*, J. Immunol 140: 837-839
(1988).

Biologically active IL-1 exists in two distinct forms, IL-1 α
with an isoelectric point of about pI 5.2 and IL-1 β with an isoelectric

- 2 -

point of about 7.0 with both forms having a molecular mass of about 17.5 kDa (Bayne *et al.*, J. Exp. Med. 163: 1267-1280 (1986) and Schmidt, J. Exp. Med. 160: 772 (1984). The polypeptides appear evolutionarily conserved, showing about 27-33% homology at the amino acid level (Clark *et al.*, Nucleic Acids Res. 14: 7897-7914 (1986).

Mammalian IL-1 β is synthesized as a cell associated precursor polypeptide with a molecular mass of about 31 kDa (Limjuco *et al.*, Proc. Natl. Acad. Sci USA 83: 3972-3976 (1986). Precursor IL-1 β is unable to bind to IL-1 receptors and is biologically inactive (Mosley *et al.*, J. Biol. Chem. 262: 2941-2944 (1987). Biological activity appears dependent upon some form of proteolytic processing which results in the conversion of the precursor 31 kDa form to the mature 17.5 kDa form. Evidence is growing that by inhibiting the conversion of precursor IL-1 β to mature IL-1 β , one can effectively inhibit the activity of interleukin-1.

Mammalian cells capable of producing IL-1 β include, but are not limited to, keratinocytes, endothelial cells, mesangial cells, thymic epithelial cells, dermal fibroblasts, chondrocytes, astrocytes, glioma cells, mono-nuclear phagocytes, granulocytes, T and B lymphocytes and natural killer cells.

As discussed by J.J. Oppenheim, *et al.*, Immunology Today, vol. 7(2):45-56 (1986), the activities of interleukin-1 are many. It has been observed that catabolin, a factor that promotes degradation of cartilage matrix, also exhibited the thymocyte co-mitogenic activities of IL-1 and stimulates chondrocytes to release matrix metalloproteinases and plasminogen activator. In addition, a plasma factor termed 'proteolysis inducing factor' stimulates muscle cells to produce prostaglandins which in turn leads to proteolysis, the release of amino acids and, in the long run, muscle wasting, and appears to represent a fragment of IL-1 with fever-inducing, acute phase response and thymocyte co-mitogenic activities.

IL-1 has multiple effects on cells involved in inflammation and wound healing. Subcutaneous injection of IL-1 leads to margination of neutrophils and maximal extravascular infiltration of the polymorphonuclear leukocytes (PMN). *In vitro* studies reveal IL-1 to be

- 3 -

a chemotactic attractant for PMN, to activate PMN to metabolize glucose more rapidly, to reduce nitroblue tetrazolium, and to release PMN lysosomal enzymes. Endothelial cells are stimulated to proliferate by IL-1 to produce thromboxane, to become more adhesive, and to release procoagulating activities. IL-1 also enhances collagen type IV production by epidermal cells, induces osteoblast proliferation and alkaline phosphatase production, and stimulates osteoclasts to resorb bone. Even macrophages have been reported to be chemotactically attracted to IL-1 to produce prostaglandins in response to IL-1 and to exhibit a more prolonged and active tumoricidal state.

IL-1 is also a potent bone resorptive agent which upon infusion into mice causes hypercalcemia and increases in bone resorptive surface as revealed by histomorphometry (Sabatini, M. *et al.*, PNAS 85: 5235-5239, 1988).

Accordingly, disease states in which the ICE inhibitors of Formula I may be useful as therapeutic agents include, but are not limited to, infectious diseases where active infection exists at any body site, such as meningitis and salpingitis; complications of infections including septic shock, disseminated intravascular coagulation, and/or adult respiratory distress syndrome; acute or chronic inflammation due to antigen, antibody, and/or complement deposition; inflammatory conditions including arthritis, cholangitis, colitis, encephalitis, endocarditis, glomerulonephritis, interstitial nephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury and vasculitis. Immune-based diseases which may be responsive to ICE inhibitors of Formula I include but are not limited to conditions involving T-cells and/or macrophages such as acute and delayed hypersensitivity, graft rejection, and graft-versus-host-disease; auto-immune diseases including Type I diabetes mellitus and multiple sclerosis. ICE inhibitors of Formula I may also be useful in the treatment of bone and cartilage resorption as well as diseases resulting in excessive deposition of extracellular matrix. Such diseases include periodontal diseases, interstitial pulmonary fibrosis, cirrhosis, systemic sclerosis, and keloid formation. ICE inhibitors of Formula I may also be useful in treatment of certain tumors which

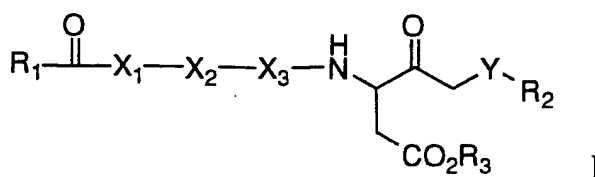
produce IL-1 as an autocrine growth factor and in preventing the cachexia associated with certain tumors.

SUMMARY OF THE INVENTION

Novel ketone derivatives of Formula I are found to be potent inhibitors of interleukin-1 β converting enzyme (ICE). Compounds of Formula I are useful in the treatment of diseases including inflammation in lung, central nervous system, kidney, joints, endocardium, pericardium, eyes, ears, skin, gastrointestinal tract and urogenital system.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula I.



or a pharmaceutically acceptable salt thereof thereof:

wherein:

R₁ is

- (a) substituted C₁-6alkyl or substituted C₁-6alkoxy, wherein the substituent is selected from
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halo which is defined to include F, Br, Cl, and I,
 - (4) C₁-3alkyloxy,
 - (5) C₁-3alkylthio,
 - (6) phenyl C₁-3alkyloxy, and
 - (7) phenyl C₁-3alkylthio;
- (b) substituted C₂-6 alkenyl or substituted C₂-6 alkenyloxy, wherein the substituent is selected from
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,

- 5 -

- (4) C₁-3alkyloxy,
(5) C₁-3alkylthio,
(6) phenyl C₁-3alkyloxy, and
(7) phenyl C₁-3alkylthio;
- 5 (c) aryl, aryl C₁-6alkyl, and aryl C₂-6alkyloxy wherein the C₁-6alkyl is optionally substituted with C₁-3alkylcarbonyl-amino, and the aryl group is selected from the group consisting of:
- 10 (1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) pyrrol,
(6) thienyl,
15 (7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
20 (12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
25 (17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
30 (22) carbazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and

- 6 -

(27) benzoxazolyl,
and mono- and di-substituted aryl as defined above in items
(1) to (27) wherein the substituents on the aryl are
independently selected from C₁-6alkyl, C₁-6alkyloxy, halo,
hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl,
carboxyl, carboxylC₁-6alkyl, and C₁-6alkylcarbonyl;

R₂ is

- (a) phenyl,
- (b) 1-naphthyl,
- (c) substituted 2-naphthyl wherein the substituents are individually selected from the group consisting of
 - (1) hydrogen,
 - (2) halo,
 - (3) C₁-6alkyl,
 - (4) perfluoro C₁-3alkyl,
 - (5) nitro,
 - (6) cyano,
 - (7) C₁-6alkylcarbonyl,
 - (8) phenylcarbonyl,
 - (9) carboxy,
 - (10) aminocarbonyl,
 - (11) mono- and di-C₁-6alkylaminocarbonyl,
 - (12) phenylaminocarbonyl,
 - (13) formyl,
 - (14) aminosulfonyl,
 - (15) C₁-6alkyl sulfonyl,
 - (16) phenyl sulfonyl,
 - (17) formamido,
 - (18) C₁-6alkylcarbonylamino,
 - (19) phenylcarbonylamino,
 - (20) C₁-6alkoxycarbonyl,
 - (21) C₁-6alkylsulfonamido carbonyl,
 - (22) phenylsulfonamido carbonyl,

- 7 -

- 5 (23) C₁-6alkyl carbonylamino sulfonyl,
(24) phenylcarbonylamino sulfonyl,
(25) C₁-6alkyl amino,
(26) C₁-3dialkyl amino,
(27) amino,
(28) hydroxy,
(29) C₁-6alkyloxy, and
(30) aryl, aryl C₁-6alkyl, and aryl C₁-6alkoxy wherein the
10 aryl group is selected from the group consisting of:
(a) phenyl,
(b) naphthyl,
(c) pyridyl,
(d) furyl,
(e) pyrrol,
15 (f) thienyl,
(g) isothiazolyl,
(h) imidazolyl,
(i) benzimidazolyl,
(j) tetrazolyl,
20 (k) pyrazinyl,
(l) pyrimidyl,
(m) quinolyl,
(n) isoquinolyl,
(o) benzofuryl,
25 (p) isobenzofuryl,
(q) benzothienyl,
(r) pyrazolyl,
(s) indolyl,
(t) isoindolyl,
30 (u) purinyl,
(v) carbazolyl,
(w) isoxazolyl,
(x) thiazolyl,
(y) oxazolyl,

- 8 -

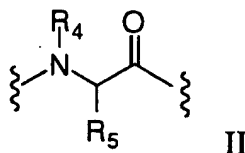
(z) benzthiazolyl, and
 (a1) benzoxazolyl,
 and mono- and di-substituted aryl or heteroaryl as
 defined above in items (a) to (a1) wherein the
 substituents are independently selected from
 C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino,
 C₁-6alkylamino, aminoC₁-6alkyl, carboxyl,
 carboxylC₁-6alkyl, and C₁-6alkylcarbonyl;

R₃ is

- (a) hydrogen,
- (b) C₁-6alkyl,
- (c) phenyl and phenyl C₁-6alkyl, and mono- and di-substituted phenyl wherein the substituents are independently selected from C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl, carboxyl, carboxyl C₁-6alkyl, and C₁-6alkylcarbonyl;

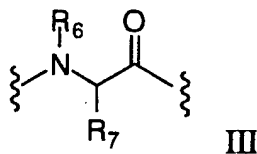
X₁ is selected from the group consisting of

- (a) a single bond, and
- (b) an amino acid of Formula II



X₂ is selected from the group consisting of

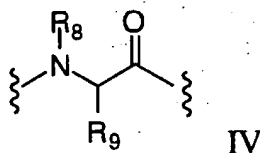
- (a) a single bond, and
- (b) an amino acid of Formula III



X₃ is selected from the group consisting of

- 9 -

- (a) a single bond, and
(b) an amino acid of Formula II



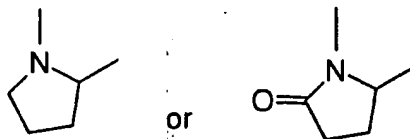
wherein R4, R5, R6, R7, R8 and R9 are independently selected from the group consisting of:

- 10 (a) hydrogen,
(b) substituted C₁-6alkyl, wherein the substituent is selected from
- 15 (1) hydrogen,
(2) hydroxy,
(3) halo,
(4) C₁-3alkylthio,
(5) thiol,
(6) C₁-6alkylcarbonyl,
(7) carboxy,
20 (8) aminocarbonyl,
(9) amino carbonyl amino,
(10) amino,
(11) C₁-3alkylamino, wherein the alkyl moiety is substituted with hydrogen or hydroxy, and
25 (12) guanidino;
- (c) aryl and aryl C₁-6alkyl wherein the aryl group is selected from the group consisting of:
- 30 (1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) pyrrol,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,

- 10 -

- 5
10
15
20
25
30
- (9) benzimidazolyl,
 - (10) tetrazolyl,
 - (11) pyrazinyl,
 - (12) pyrimidyl,
 - (13) quinolyl,
 - (14) isoquinolyl,
 - (15) benzofuryl,
 - (16) isobenzofuryl,
 - (17) benzothienyl,
 - (18) pyrazolyl,
 - (19) indolyl,
 - (20) isoindolyl,
 - (21) purinyl,
 - (22) carbazolyl,
 - (23) isoxazolyl,
 - (24) thiazolyl,
 - (25) oxazolyl,
 - (26) benzthiazolyl, and
 - (27) benzoxazolyl,
- and mono- and di-substituted aryl or heteroaryl as defined above in items (1) to (27) wherein the substituents are independently selected from C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl, carboxyl, carboxylC₁-6alkyl, and C₁-6alkylcarbonyl;
- (d) R₄ and R₅, R₆ and R₇, and R₈ and R₉ may be joined, such that together with the nitrogen atom to which R₄ (or R₆ or R₈) is attached there is formed a mono-cyclic saturated ring of 5 to 8 atoms, said ring having exactly one hetero atom which is nitrogen, said ring optionally having an oxo group, said ring including,

- 11 -



5

Y is O, S, or NH.

One class of this genus is the compounds wherein:

R₁ is

10

- (a) substituted C₁-6alkyl or substituted C₁-6alkoxy, wherein the substituent is selected from

15

- (1) hydrogen,
- (2) hydroxy,
- (3) chloro or fluoro,
- (4) C₁-3alkyloxy, and
- (5) phenyl C₁-3alkyloxy,

- (b) aryl C₁-6alkyl wherein the aryl group is selected from the group consisting of

20

- (1) phenyl,
- (2) naphthyl,
- (3) pyridyl,
- (4) furyl,
- (5) thienyl,
- (6) thiazolyl,
- (7) isothiazolyl,
- (8) benzofuryl,
- (9) benzothieryl,
- (10) indolyl,
- (11) isooxazolyl, and
- (12) oxazolyl,

25

30

and mono- and di-substituted aryl as defined above in items (1) to (12) wherein the substituents are independently C₁-4alkyl, halo, and hydroxy;

R₄ is hydrogen and R₅ is selected from the group consisting of

- (a) hydrogen,

- 12 -

- (b) substituted C₁-6alkyl, wherein the substituent is selected from
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,
 - (4) C₁-4alkyl thio
 - (5) thiol
 - (6) C₁-6alkylcarbonyl,
 - (7) carboxy,
 - (8) aminocarbonyl,
 - (9) C₁-4alkylamino, and C₁-4alkylamino wherein the alkyl moiety is substituted with an hydroxy, and
 - (10) guanidino,
 - (11) C₁-4alkyloxy,
 - (12) phenylC₁-4alkyloxy,
 - (13) phenylC₁-4alkylthio, and
- (c) aryl C₁-6alkyl, wherein the aryl group is elected from the group consisting of
- (1) phenyl,
 - (2) naphthyl,
 - (3) pyridyl,
 - (4) furyl,
 - (5) thienyl,
 - (6) thiazolyl,
 - (7) isothiazolyl,
 - (8) benzofuryl,
 - (9) benzothienyl,
 - (10) indolyl,
 - (11) isooxazolyl, and
 - (12) oxazolyl,

and wherein the aryl may be mono- and di-substituted, the substituents being each independently C₁-6alkyl, halo, hydroxy, C₁-6alkyl amino, C₁-6alkoxy, C₁-6alkylthio, and C₁-6alkylcarbonyl;

- 13 -

R6, R7, R8 and R9 are each independently selected from the group consisting of

- (a) hydrogen,
- (b) C₁-6 alkyl, wherein the substituent is selected from
 - (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,
 - (4) -S-C₁-4alkyl,
 - (5) -SH,
 - (6) C₁-6alkylcarbonyl,
 - (7) carboxy,
 - (8) aminocarbonyl,
 - (9) C₁-4alkylamino, and C₁-4alkyl amino wherein the alkyl moiety is substituted with an hydroxy, and
 - (10) guanidino, and
- (c) aryl C₁-6alkyl, wherein aryl is defined as immediately above, and wherein the aryl may be mono- and di-substituted, the substituents being each independently C₁-6alkyl, halo, hydroxy, C₁-6alkyl amino, C₁-6alkoxy, C₁-6alkylthio, and C₁-6alkylcarbonyl.

Within this class are the compounds wherein X₁, X₂ and X₃, are each independently selected from the group consisting of the L- and D- forms of the amino acids including glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxy-lysine, histidine, arginine, phenyl-alanine, tyrosine, tryptophan, cysteine, methionine, ornithine, β -alanine, homoserine, homotyrosine, homophenylalanine and citrulline.

Alternatively, within this class are the subclass of compounds wherein R₁ is C₁-3alkyl, C₁-3alkenyl, C₁-3alkoxy or C₁-3alkenyloxy ; R₆, R₇, R₈ and R₉ are each individually

- (a) hydrogen,
- (b) C₁-6alkyl,

- 14 -

- 5
- (c) mercapto C₁₋₆alkyl,
 - (d) hydroxy C₁₋₆alkyl,
 - (e) carboxy C₁₋₆alkyl,
 - (g) aminocarbonyl C₁₋₆alkyl,
 - (h) mono- - or di-C₁₋₆alkyl amino C₁₋₆alkyl,
 - (i) guanidino C₁₋₆alkyl,
 - (j) amino-C₁₋₆alkyl or N-substituted amino-C₁₋₆alkyl wherein the substituent is carbobenzoxy,
 - 10 (k) carbamyl C₁₋₆alkyl, or
 - (l) aryl C₁₋₆alkyl, wherein the aryl group is selected from phenyl and indolyl, and the aryl group may be substituted with hydroxy, C₁₋₃ alkyl.

15 Exemplifying the invention are the following compounds:

- a) N-Allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic acid.
- b) N-Allyloxycarbonyl-3-amino-5-(1-naphthyloxy)-4-oxopentanoic acid.
- 20 c) N-Allyloxycarbonyl-3-amino-5-(2-naphthyloxy)-4-oxopentanoic acid.
- d) N-Allyloxycarbonyl-3-amino-5-(3-aminocarbonyl-2-naphthyloxy)-4-oxopentanoic acid.
- e) N-Allyloxycarbonyl-3-amino-5-(3-(N-phenyl)amino-carbonyl-2-naphthyloxy)-4-oxopentanoic acid.
- 25 f) N-Allyloxycarbonyl-3-amino-5-(3-cyano-2-naphthyloxy)-4-oxopentanoic acid.
- g) N-Allyloxycarbonyl-3-amino-5-(3-hydroxymethyl-2-naphthyloxy)-4-oxopentanoic acid.
- 30 h) N-Allyloxycarbonyl-3-amino-5-(3-methoxycarbonyl-2-naphthyloxy)-4-oxopentanoic acid.
- i) N-Allyloxycarbonyl-3-amino-5-(3-imidazolyl-2-naphthyloxy)-4-oxopentanoic acid.
- j) N-(N-Acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alaninyl)-3-amino-5-phenoxy-4-oxopentanoic acid.

- 15 -

- k) N-(N-Carbobenzyloxy-(L)-valinyl-(L)-alaninyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid, triethylamine salt.
- l) N-(N-Carbobenzyloxy-(L)-valinyl-(L)-prolinyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid.
- m) N-(2-indoloyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid.

This invention also concerns to pharmaceutical composition and methods of treatment of interleukin-1 and interleukin-1 β mediated or implicated disorders or diseases (as described above) in a patient (including man and/or mammalian animals raised in the dairy, meat, or fur industries or as pets) in need of such treatment comprising administration of interleukin-1 β inhibitors of Formula (I) as the active constituents.

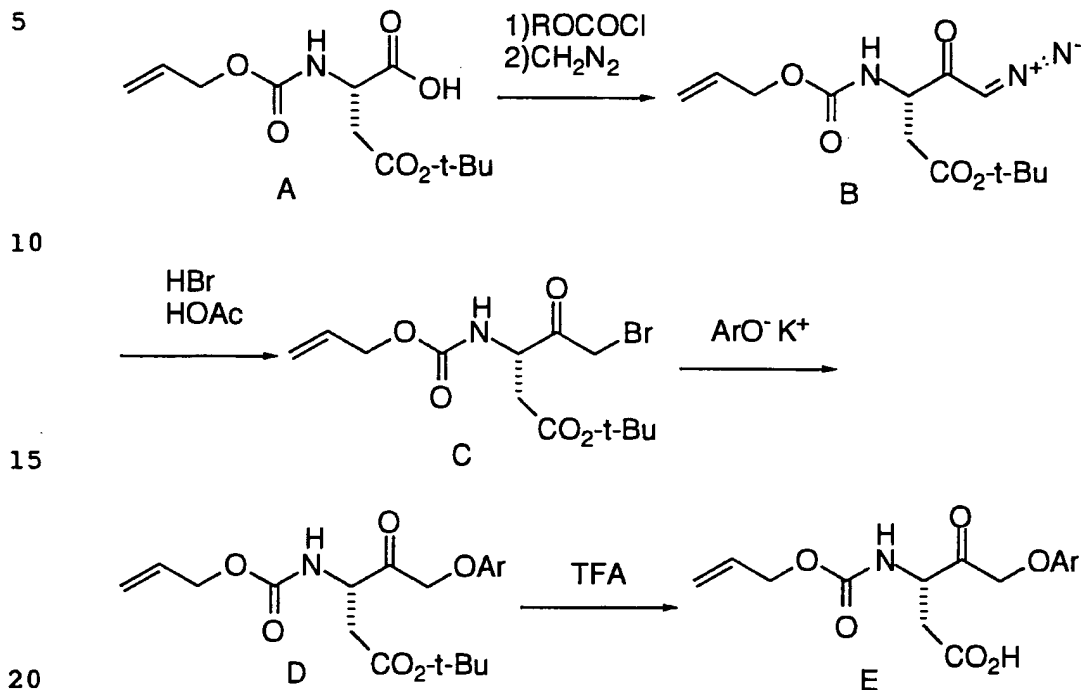
Illustrative of these aspects, this invention concerns pharmaceutical compositions and methods of treatment of diseases selected from septic shock, allograft rejection, inflammatory bowel disease and rheumatoid arthritis in a patient in need of such treatment comprising:

administration of an interleukin-1 β converting enzyme inhibitor of Formula (I) as the active constituent.

Compounds of the instant invention have are particularly useful in the treatment of ICE mediated diseases advantageously treated with agents that are selective inhibitors of ICE. For example, structurally related compounds such as those disclosed in U.S. 5,055,451, issued to Krantz *et. al.*, October 8, 1991 by design inhibit cathepsin B. Compounds of the instant invention are selective inhibitors of ICE over Cathepsin B. For purposes of this specification a compound is to be considered selective for ICE over Cathepsin B if the ratios of the IC₅₀ for ICE to the IC₅₀ for Cathepsin B is 0.01 or smaller.

- 16 -

Compounds of the instant invention are conveniently prepared using the procedures described generally below and more explicitly described in the Example section thereafter.



The described compounds can be prepared as follows:

An appropriately N-protected aspartic acid ester A is first treated with an alkyl chloroformate to form the mixed anhydride *in situ* which is subsequently reacted with excess diazomethane to form the diazomethyl ketone B. Subsequent reaction of B with hydrobromic acid in acetic acid forms the bromomethyl ketone C. Reaction of C with a metal salt of a desired aryloxy compound affects displacement of the bromide to form the aryloxymethyl ketone D. Removal of the t-butyl ester with strong acid (trifluoroacetic acid or hydrochloric acid) will give the desired final product E. *In situ* removal of the 'Alloc' protecting group with a palladium catalyst and alkyltin hydride in the presence of a carboxylic acid or N-protected amino acid or peptide and a suitable condensing agent(s) will provide other examples.

25

30

- 17 -

The compounds of the instant invention of the Formula (I), as represented in the Examples hereinunder shown to exhibit *in vitro* inhibitory activities with respect to interleukin-1 β . In particular, these compounds have been shown to inhibit interleukin-1 β converting enzyme
5 from cleaving precursor interleukin-1 β as to form active interleukin-1 β .

Compounds of the instant invention of Formula (I) are evaluated *in vivo* by inhibiting LPS-induced fever in rats and by reducing inflammation in carrageenan-induced paw edema in rats by methodology described by R. Heng, T. Payne, L. Revesz, B. Weidmann in PCT
10 WO93/09135 (published 13 May 1993).

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat, or fur industries or as pets) suffering from disorders or diseases which can be attributed to IL-1/ICE as previously described, and more
15 specifically, a method of treatment involving the administration of the IL-1/ICE inhibitors of Formula (I) as the active constituents.

Accordingly, disease states in which the ICE inhibitors of Formula I may be useful as therapeutic agents include, but are not limited to, infectious diseases where active infection exists at any body site, such
20 as meningitis and salpingitis; complications of infections including septic shock, disseminated intravascular coagulation, and/or adult respiratory distress syndrome; acute or chronic inflammation due to antigen, antibody, and/or complement deposition; inflammatory conditions including arthritis, cholangitis, colitis, encephalitis, endocarditis,
25 glomerulonephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury and vasculitis. Immune-based diseases which may be responsive to ICE inhibitors of Formula I include but are not limited to conditions involving T-cells and/or macrophages such as acute and delayed hypersensitivity, graft rejection, and graft-versus-host-disease;
30 auto-immune diseases including Type I diabetes mellitus and multiple sclerosis. ICE inhibitors of Formula I may also be useful in the treatment of bone and cartilage resorption as well as diseases resulting in excessive deposition of extracellular matrix such as interstitial pulmonary fibrosis, cirrhosis, systemic sclerosis, and keloid formation. ICE inhibitors of

- 18 -

Formula I may also be useful in treatment of certain tumors which produce IL 1 as an autocrine growth factor and in preventing the cachexia associated with certain tumors.

5 For the treatment the above mentioned diseases, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes
10 subcutaneous injections, intravenous, intramuscular, intracisternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active
15 ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical
20 compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically
25 acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic
30 acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be

- 19 -

coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

5 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

10 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring
15 phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and
20 a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan mono-oleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring
25 agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The
30 oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

- 20 -

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

- 21 -

The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 2.5 mg to about 7 gms. per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 gms per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

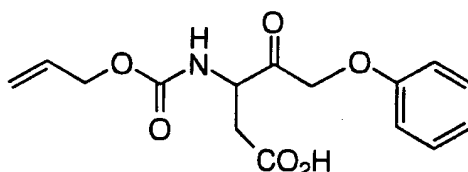
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples are intended to illustrate the preparation of compounds of Formula I, and as such are not intended to limit the invention as set forth in the claims appended, thereto.

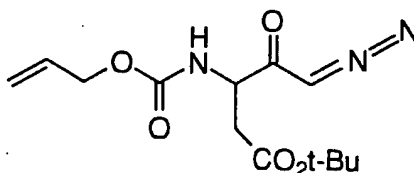
Additional methods of making compounds of this invention are known in the art such as U.S. 5,055,451, issued to Krantz *et al.*, October 8, 1991 which is hereby incorporated by reference.

EXAMPLE 1

N-Allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic acid



Step A: N-Allyloxycarbonyl-3-amino-5-diazo-4-oxopentanoic acid, t-butyl ester

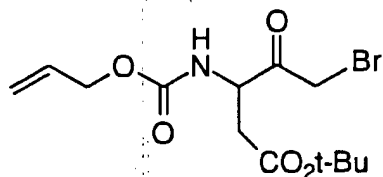


To a solution of N-allyloxycarbonyl-(L)-aspartic acid, β -t-butyl ester (6.23 g, 22.8 mmol) and 4-methyl morpholine (2.63 mL, 23.94 mmol) in 50 mL of freshly distilled dichloromethane at -10°C was added freshly distilled isobutyl chloroformate (3.04 mL, 23.48 mmol). After 15 min, the solution was filtered and excess ethereal diazomethane was added. The mixture was stirred at 0°C for 1 h and concentrated. The mixture was purified by medium pressure liquid chromatography (MPLC) on silica-gel (35 x 350 mm column, eluting with 25% ethyl acetate in hexane) to give the title compound as a pale yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 5.91 (1H, m), 5.62 (1H, br s), 5.31 (1H, d), 5.24 (1H, d), 4.61 (2H, br d), 4.50 (1H, m), 2.92 (1H, dd), 2.60 (1H, dd), 1.43 (9H, s).

- 23 -

Step B: N-Allyloxycarbonyl-3-amino-5-bromo-4-oxopentanoic acid,
t-butyl ester

5



10

To a solution of N-allyloxycarbonyl-3-amino-5-diazo-4-oxopentanoic acid, β -t-butyl ester in ether was added approximately one equivalent of hydrobromic acid (30% in acetic acid). After 30 min, the solution was diluted with ether and washed three times with water. The combined organic layers were dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The product was purified by MPLC on silica gel eluted with 20% ethyl acetate in hexane to afford the title compound as a colorless solid:

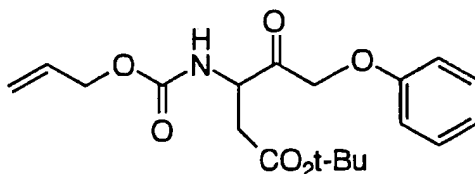
15

^1H NMR (400 MHz, CD_3OD) δ 5.93 (1H, m), 5.31 (1H, d), 5.19 (1H, d), 4.69 (1H, t), 4.58 (2H, br d), 4.29 (2H, ABX), 2.82 (1H, dd), 2.63 (1H, dd), 1.43 (9H, s).

20

Step C: N-Allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic acid, t-butyl ester

25



30

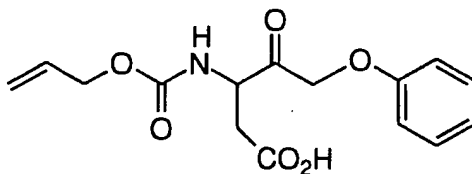
To a solution of phenol (59 mg, 0.628 mmol) in dimethylformamide (5 ml) was added potassium carbonate (87 mg, 0.628 mmol). The mixture was stirred for 5 min, followed by addition of N-allyloxy-3-amino-5-bromo-4-oxo-pentanoic acid, β -t-butyl ester (200 mg, 0.571 mmol). The mixture was stirred for 16 hours at room temperature, then diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and

- 24 -

filtered. The solvent was removed *in vacuo* and the product purified by flash column chromatography on silica gel eluted with 20% t-butyl methyl ether in hexane to provide the title compound.

5 ^1H NMR (CD_3OD) δ 7.25 (2H, m), 6.92 (3H, m), 5.9 (1H, m), 5.22 (2H, m), 4.9 (2H, ABX), 4.7 (1H, t), 4.55 (2H, dd), 2.85 (1H, dd), 2.7 (1H, dd), 1.45 (9H, s).

10 Step D: N-Allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic acid



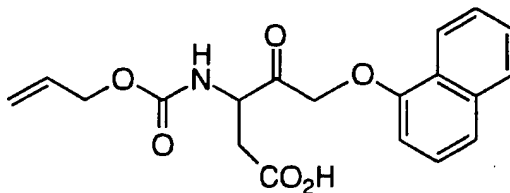
15 N-allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic acid, t-butyl ester from Step C (170 mg, 0.467 mmol) was dissolved in dichloromethane (8 ml) and trifluoroacetic acid (8 ml) under nitrogen. The resulting mixture was stirred for 15 minutes. The solvent was reduced *in vacuo* to provide the target compound.

20 ^1H NMR (CDCl_3) δ 7.3 (2H, m), 6.92 (3H, m), 5.45 (1H, br.s), 5.2 (2H, m), 4.6 (1H, bs), 4.52 (2H, d), 4.2 (2H, br.s), 2.95 (2H, dbr.); mass spectrum: m/e 308($\text{M}+1$) $^+$, 263.9, 213.7, 106.7, 154.7, 119.0.

25 By following the procedures described in Example 1, Examples 2-9 may be prepared:

EXAMPLE 2

30 N-Allyloxycarbonyl-3-amino-5-(1-naphthyloxy)-4-oxopentanoic acid

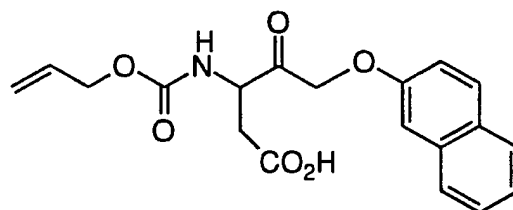


- 25 -

¹H NMR(CDCl₃) δ 7.8(1H, m), 7.49(3H, m), 7.31(1H, m), 7.25 (1H, m), 7.15 (1H, m), 5.89 (1H, m), 5.25 (2H, m), 5.0 (2H, ABX), 4.68 (1H, m), 4.55 (2H, m), 3.2 (1H, dd), 3.0 (1H, ddd); mass spectrum: m/e 380 (M+Na)⁺, 358.1 (M+1)⁺, 338.8, 196.7, 176.7, 143.9, 119.1.

EXAMPLE 3

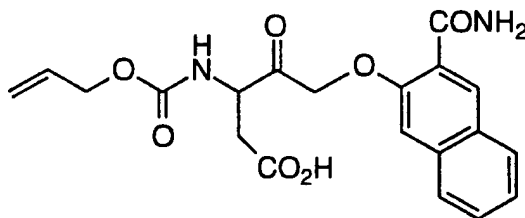
N-Allyloxycarbonyl-3-amino-5-(2-naphthyloxy)-4-oxopentanoic acid



¹H NMR(CDCl₃) δ 7.72 (3H, m), 7.42 (1H, m), 7.35 (1H, m), 7.15 (2H, m), 5.85 (1H, m), 5.25 (2H, m), 5.0 (1H, m), 4.82 (2H, br.s), 4.59 (2H, m), 3.2-2.6 (2H, m); mass spectrum: m/e 380(M+Na)⁺, 358.1 (M+1)⁺, 338.8, 196.7, 176.7, 143.9, 119.1.

EXAMPLE 4

N-Allyloxycarbonyl-3-amino-5-(3-aminocarbonyl-2-naphthyloxy)-4-oxopentanoic acid

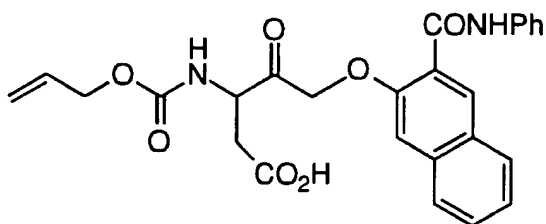


¹H NMR (CD₃OD) δ 7.52 (2H, m), 7.35 (2H, m), 5.9 (1H, m), 5.85 (2H, q), 5.2 (2H, m), 4.72-4.15 (5H, br, m), 2.9 (2H, m); mass spectrum: m/e 423.0 (M+Na)⁺, 401.8 (M+1)⁺, 383.8, 365.9, 325.9, 187.7, 170.7, 134.9.

- 26 -

EXAMPLE 5

5 N-Allyloxycarbonyl-3-amino-5-(3-(N-phenyl)aminocarbonyl-2-naphthyloxy)-4-oxopentanoic acid

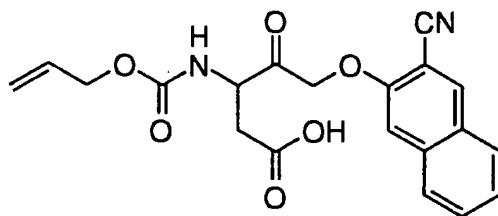


^1H NMR (CDCl_3) δ 7.8 (1H, m), 7.69 (1H, m), 7.45 (2H, m), 7.25 (4H, br m), 7.06 (1H, m), 6.05 (1H, m), 5.9 (1H, m), 5.62 (1H, NH), 5.2 (2H, m), 5.0 (1H, m), 4.7-4.38 (4H, m), 3.1-2.8 (2H, m); mass spectrum: m/e 499.7 ($\text{M}+\text{Na}$) $^+$, 477.6 ($\text{M}+1$) $^+$, 459.4, 366.1, 264.0, 182.7, 170.7, 141.9, 115.2.

15

EXAMPLE 6

20 N-Allyloxycarbonyl-3-amino-5-(3-cyano-2-naphthyloxy)-4-oxopentanoic acid



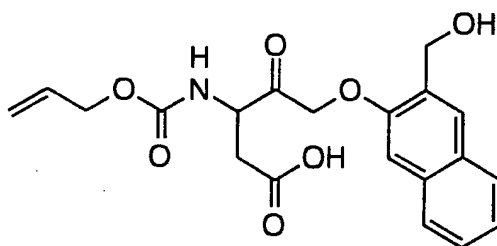
^1H NMR (400MHz, CDCl_3) δ 8.10 (1H, s), 7.75 (2H, m), 7.58 (2H, m), 7.42 (2H, m), 5.88 (1H, m), 5.15-5.38 (2H, m), 4.85 (2H, s), 4.58 (2H, m), 4.40 (1H, m); mass spectrum: m/e $\text{M}+1$ (383.1), 365.1, 169.1, 112.1.

30

- 27 -

EXAMPLE 7

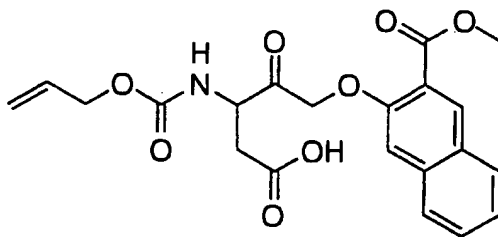
N-Allyloxycarbonyl-3-amino-5-(3-hydroxymethyl-2-naphthyloxy)-4-oxopentanoic acid



^1H NMR (400MHz, CDCl_3) δ 7.50 (3H, m), 7.42 (2H, m), 7.05 (1H, s), 5.83 (1H, m), 5.20 (2H, m), 4.70-4.92 (2H, m), 4.20-4.61 (5H, br m), 2.60-3.01 (2H, m); mass spectrum: m/e $\text{M}+\text{K}^+$ (426.0), $\text{M}+\text{Na}^+$ (410.0), M^+ (387.0) 369.9, 352.0, 269.0, 239.0.

EXAMPLE 8

N-Allyloxycarbonyl-3-amino-5-(3-methoxycarbonyl-2-naphthyloxy)-4-oxopentanoic acid

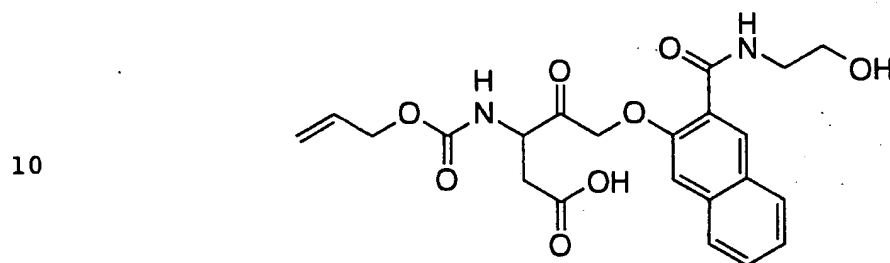


^1H NMR (400MHz, CDCl_3) δ 8.39 (1H, s), 7.82 (1H, d), 7.72 (1H, d), 7.55 (1H, t), 7.42 (2H, m), 7.23 (1H, s), 5.85 (1H, m), 5.50 (1H, s), 5.10-5.40 (1H, m), 4.42-4.70 (4H, m), 4.25 (1H, m), 3.95 (3H, s), 2.75-2.98 (2H, m); mass spectrum: m/e $\text{M}+\text{Na}^+$ (438), $\text{M}+1$ (416), 384, 326, 214, 202, 171, 170.

- 28 -

EXAMPLE 9

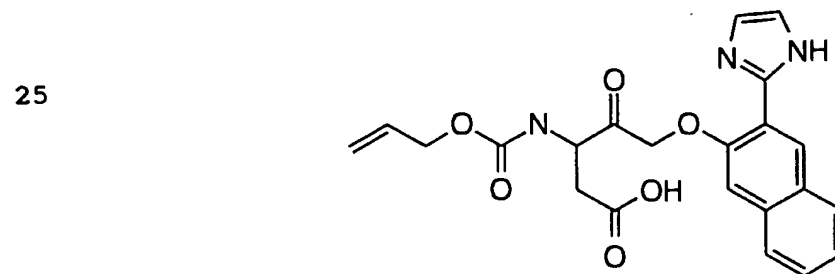
5 N-Allyloxycarbonyl-3-amino-5-(3-(2-hydroxyethyl-1-aminocarbonyl)-2-naphthyloxy)-4-oxopentanoic acid



15 ¹H NMR (200 MHz, CD₃OD) δ 8.49 (1H, s), 7.75-7.93 (2H, m), 7.31-7.57 (4H, m), 5.90 (1H, m), 5.00-5.38 (2H, m), 4.18-4.79 (5H, m), 3.82 (2H, t), 3.65 (2H, t), 2.90 (2H, m); mass spectrum: m/e M+1 (444.9), 394.1, 278.9, 218.9, 202.9.

EXAMPLE 10

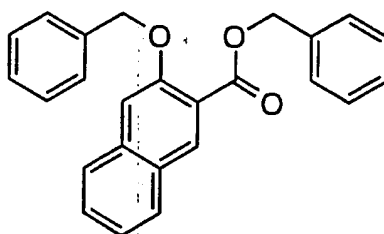
20 N-Allyloxycarbonyl-3-amino-5-(3-imidazolyl-2-naphthyloxy)-4-oxopentanoic acid



30

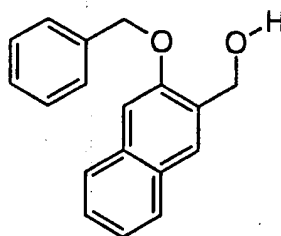
- 29 -

Step A: 3-Benzyloxy-naphthalene-2-carboxylic acid, benzyl ester



To a solution of 3-hydroxy-naphthalene-2-carboxylic acid (3.76 g, 20 mmol) in dimethylformamide, at 0°C, was added sodium hydride (1.01 g, 42 mmol) 15 minutes later, freshly distilled benzyl bromide (4.98 ml, 42 mmol) was added. After stirring at room temperature under nitrogen for 16 hours, the solution was diluted with ethyl acetate and washed twice with 2N aqueous hydrochloric acid. The organic layer was then dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide the title compound (7.12 g).

Step B: (3-Benzyloxy-2-naphthyl)methyl alcohol

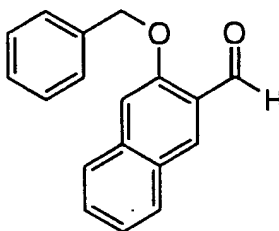


To a solution of 3-benzyloxy-naphthalene-2-carboxylic acid, benzyl ester (7.12 g, 19.34 mmol) in dry dichloromethane at -78°C was dropwise added diisobutylaluminum hydride (DIBAL-H) (27 ml of 1.5M solution in toluene, 40.6 mmol). The reaction was warmed to room temperature after one hour. Sixteen hours later, the reaction was cooled to 0°C and was quenched carefully with water. The mixture was diluted with ethyl acetate and washed twice with 2N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate, filtered and then

- 30 -

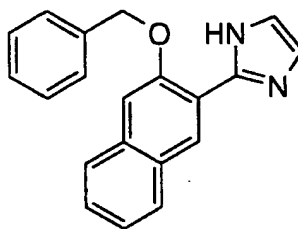
concentrated *in vacuo*. The residue was eluted through silica gel with dichloromethane to give the title compound (3.2 g).

5 Step C: 3-Benzyloxy-naphthalene-2-carboxaldehyde



10 To a solution of (3-benzyloxy-2-naphthyl)methyl alcohol (3.2 g, 12.12 mmol) in dichloromethane was added 4Å molecular sieves (6.06 g) and 4-methylmorpholine N-oxide (2.13 g, 18.18 mmol). After 5 minutes, tetrapropylammonium perruthenate (TPAP) (606 mg) was added and the mixture was stirred at room temperature for 3 hours. The mixture was filtered through silica gel eluted with dichloromethane. The eluate was concentrated *in vacuo* to give the title compound (2.45 g).

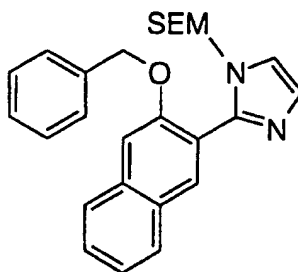
20 Step D: 2-Benzyloxy-3-(2-imidazolyl)naphthalene



25 3-Benzyloxy-naphthalene-2-carboxaldehyde (90 mg, 0.34 mmol) and trimeric glyoxal dihydrate (210 mg, 1.02 mmol) were dissolved in 10 ml methanol. The solution was vigorously stirred as concentrated ammonium hydroxide (2 ml) was then slowly added. After 16 hours, the solution was concentrated *in vacuo*. The residue was eluted with 10% ethyl acetate in hexane through a pad of silica gel to give the title compound (62 mgs).

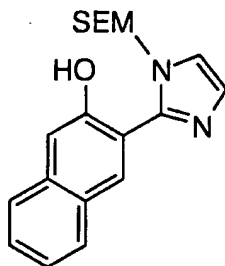
- 31 -

Step E: 2-Benzyloxy-3-(1-(2-trimethylsilylethoxymethyl)-2-imidazolyl)-naphthalene



To the solution of 2-benzyloxy-3-(2-imidazolyl)naphthalene (62 mgs, 0.206 mmol) in dry dimethylformamide was slowly added sodium hydride (5.2 mg, 0.216 mmol). After 1 hour, 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) (40 ul, 0.227 mmol) was added and the mixture was stirred under nitrogen for 3 hours. The solution was diluted with ethyl acetate and washed 3 times with water. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The yellow solid was eluted with 20% ethyl acetate in hexane through a pad of silica gel to give the the title compound (40 mgs).

Step F: 3-(1-(2-trimethylsilylethoxymethyl)-2-imidazolyl)-2-naphthol

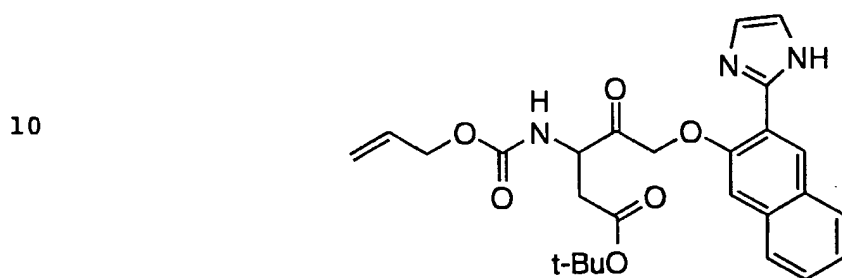


2-Benzyloxy-3-(1-(2-trimethylsilylethoxymethyl)-2-imidazolyl)naphthalene (40 mg) and Pd/C (50 mg) was dissolved in 10 ml methanol. The mixture was stirred vigorously under one atmosphere of hydrogen for 2 hours. The mixture was filtered through celite filter aid, the pad washed with fresh methanol, and the combined eluents

- 32 -

concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with 5% acetone in hexane to afford the title compound (24 mgs).

5 Step G: N-Allyloxycarbonyl-3-amino-5-(3-imidazolyl-2-naphthyloxy)-4-oxopentanoic acid, t-butyl ester



15 Potassium carbonate (10 mg, 0.071 mmol) and 3-(1-(2-trimethylsilylethoxymethyl)-2-imidazolyl)-2-naphthol (24 mg, 0.071 mmol) were stirred in dimethylformamide (5 ml) under nitrogen for 5 minutes. N-Allyloxycarbonyl-3-amino-5-bromo-4-oxopentanoic acid, t-butyl ester (25 mg, 0.071 mmol) was then added and the mixture was

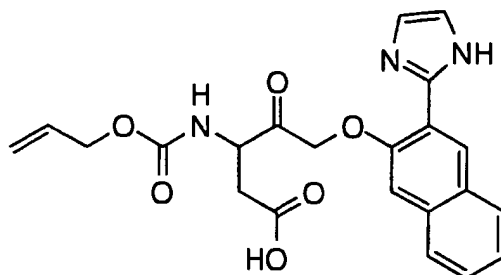
20 stirred for 16 hours at room temperature under nitrogen atmosphere. The mixture was diluted with ethyl acetate and was successively washed three times with saturated aqueous sodium carbonate solution. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The yellow oil was purified by column chromatography on silica gel

25 eluted with 20% t-butyl methyl ether in hexane to give the title compound (22 mgs).

30 Step H: N-Allyloxycarbonyl-3-amino-5-(3-imidazolyl-2-naphthyloxy)-4-oxopentanoic acid

- 33 -

5



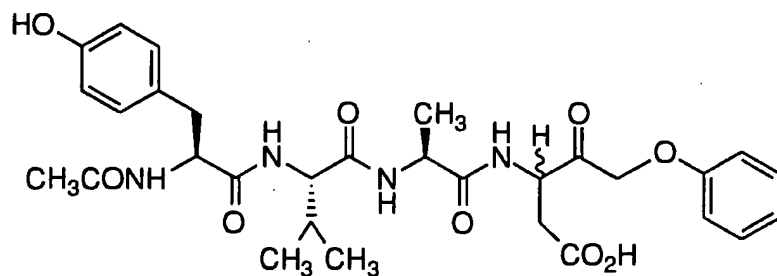
10 N-Allyloxycarbonyl-3-amino-5-(3-imidazolyl-2-naphthoxy)-4-oxopentanoic acid, t-butyl ester (22 mg, 0.0360 mmol) was dissolved in dichloromethane (8 ml) and trifluoroacetic acid (8 ml) under nitrogen. After 15 minutes, the solution was concentrated *in vacuo* to afford the title compound (15 mg):
¹H NMR (400 MHz, CD₃OD) δ 8.45 (1H, s), 7.85 (1H, d), 7.78 (1H, d), 7.50 (2H, m), 7.41 (3H, m), 5.50 (1H, m), 5.15-5.38 (4H, m), 4.71 (1H, m), 4.60 (2H, m); mass spectrum: m/e M+1 (424.3), 394.5, 172.1, 119.1, 98.1, 86.1.

EXAMPLE 11

20

N-(N-Acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alaninyl)-3-amino-5-phenoxy-4-oxopentanoic acid

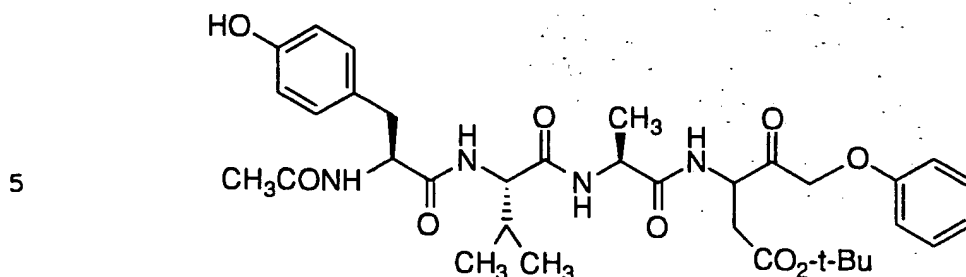
25



30

Step A: N-(N-Acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alaninyl)-3-amino-4-oxo-5-phenoxy-pentanoic acid, t-butyl ester

- 34 -



10 To a solution of N-allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic acid, t-butyl ester (from Step C, Example 1) (86 mg, 0.24 mmol) in a 1:1 mixture of dichloromethane:dimethylformamide (6 ml) was added N-acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alanine (87 mg, 0.26 mmol), N-hydroxybenztriazole (38 mg, 0.28 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (50 mg, 0.26 mmol) and bis(triphenylphosphine) palladium(II) chloride (10 mg). To

15 the stirred mixture, tributyltin hydride (76 ul, 0.28 mmol) was added dropwise. After 16 hours, the mixture was diluted with ethyl acetate and successively washed with 2N hydrochloric acid and saturated sodium bicarbonate solution. The solution was dried over anhydrous sodium

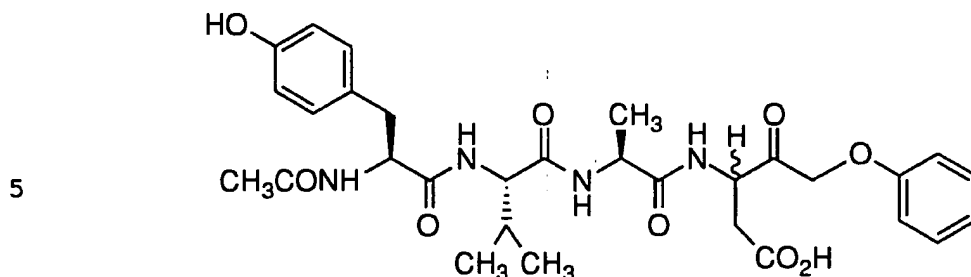
20 sulfate and the solvent was reduced *in vacuo*. The product was purified by flash column chromatography on silica gel eluted with 5% methanol in dichloromethane to give the title compound.

25 ¹H NMR (CD₃OD) δ 7.25 (2H, t), 7.05 (2H, m), 6.95 (3H, m), 6.66 (2H, m), 5.0 (2H, m), 4.75 (1H, tt), 4.55 (1H, m), 4.32 (1H, m), 4.15 (1H, m), 3.1-2.6 (4H, complex), 2.05 (1H, m), 1.98 (3H, ss), 1.42 (9H, s), 1.37 (3H, m), 0.95 (9H, m).

Step B: N-(N-Acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alaninyl)-3-amino-4-oxo-5-phenoxy-pentanoic acid

30

- 35 -



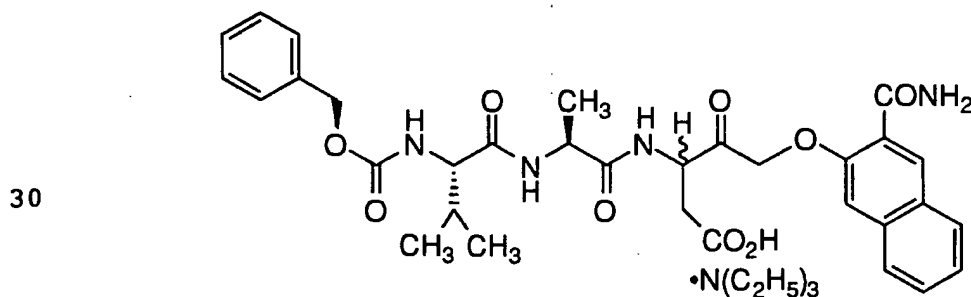
10 N-(N-Acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alaninyl)-3-amino-4-oxo-5-phenoxy-pentanoic acid, t-butyl ester (56 mg, 0.086 mmol) was dissolved in a 1:1 mixture of dichloromethane and trifluoroacetic acid (20 ml). The mixture was stirred for 15 minutes and then the solvent was reduced *in vacuo* to afford the title compound.

15 ^1H NMR (CD_3OD), δ 7.25 (2H, m), 7.05 (2H, m), 6.95 (3H, m), 6.7 (2H, m), 5.0 (2H, m), 4.72 (1H, tt), 4.58 (1H, m), 4.3 (1H, m), 4.15 (1H, m), 3.1-2.7 (4H, complex), 2.03 (1H, m), 1.89 (3H, m), 1.37 (3H, m), 0.97 (9H, m); mass spectrum: m/e 636.9 ($\text{M}+\text{K}$) $^+$, 599.4 ($\text{M}+1$) $^+$, 545.5, 393.8, 375.9, 304.9, 294.9, 205.7, 177.7.

20 By following the procedures described in Example 11, Examples 12-14 may be prepared:

EXAMPLE 12

25 N-(N-Carbobenzyloxy-(L)-valinyl-(L)-alaninyl)-3-amino-5-(3-amino-carbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid, triethylamine salt



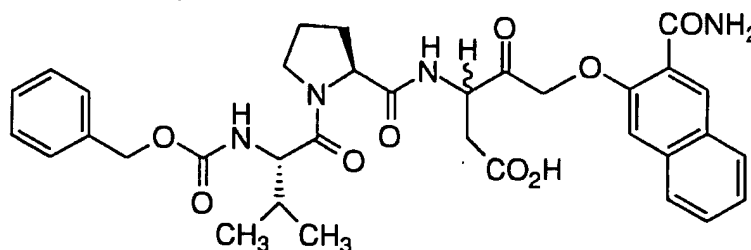
^1H NMR (CD_3OD) δ 7.84 (2H, m), 7.6-7.2 (8H, m), 5.50-5.15 (2H, m), 5.08 (2H, br s), 4.74 (1H, m), 4.40 (1H, m), 3.90 (1H, m), 2.98 (6H, q),

- 36 -

2.90-2.65 (2H, m), 2.08 (1H, br m), 1.41 (3H, d), 1.20 (9H, t), 0.93 (6H, m).

EXAMPLE 13

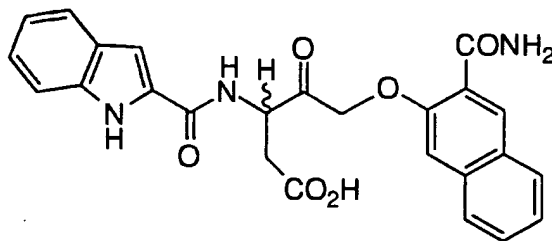
N-(N-Carbobenzyloxy-(L)-valinyl-(L)-prolinyl)-3-amino-5-(3-amino-carbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid



^1H NMR (CD_3OD) δ 7.87 (2H, m), 7.66 (2H, m), 7.55 (2H, m), 7.49-7.25 (5H, m), 5.40, 5.20 (2H, ABq), 5.08 (2H, br s), 4.63, 4.45 (1H, t), 4.30, 4.11 (1H, m), 3.90, 3.70 (1H, br m), 3.11-2.80 (2H, m), 2.26 (1H, br m), 2.17-1.80 (2H, br m), 1.08-0.84 (6H, m), 0.80 (2H, d), 0.68 (2H, d).

EXAMPLE 14

N-(2-indoloyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid



^1H NMR (CD_3OD) δ 7.85-7.0 (11H, m), 5.33 (2H, ABq), 5.15 (1H, t), 3.18, 2.95 (2H, dd).

- 37 -

EXAMPLE 15.Inhibition of Interleukin-1 β Converting Enzyme (ICE).

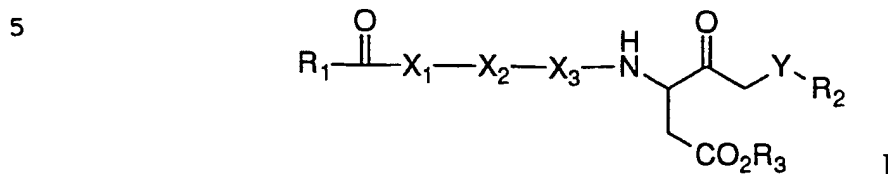
5 A fluorometric assay used to evaluate the inhibition of interleukin-1 β converting enzyme (ICE) hydrolysis of a peptide substrate (Ac-Tyr-Val-Ala-Asp-AMC) by the compounds described in Examples 1-15 has been described in detail (N. A. Thornberry et al., *Nature* **1992**, 356, 768-774). Briefly, liberation of AMC (aminomethylcoumarin) from the substrate
 10 was monitored continuously in a spectrofluorometer using an excitation wavelength of 380 nm and an emission wavelength of 460 nm. Details for determining kinetic constants for reversible and irreversible inhibition are described (N. A. Thornberry et al., *Biochemistry* **1994**, 33, 3934-3940).

15 Inhibition of Interleukin-1 β Converting Enzyme (ICE) by Examples 1-14

	Example No.	K _i (μ M) (\pm S.E.)		k _{on} (M ⁻¹ s ⁻¹) (\pm S.E.)	
20	1	3.5	(0.6)		
	2	9.5	(2.)		
	3	5.0	(1.)		
	4	0.3	(0.1)		
	5	0.5	(0.1)		
25	6	0.62	(0.1)	4500	(900)
	7	1.2	(0.2)		
	8	2.6	(0.5)		
	9	0.52	(0.1)	1000	(200)
	10	0.09	(0.02)	12,000	(2,400)
30	11	0.003	(0.0005)		
	12			430,000	(86,000)
	13			340,000	(68,000)
	14			390	(78)

WHAT IS CLAIMED IS:

1. The invention encompasses compounds of Formula I.



10 or a pharmaceutically acceptable salt thereof thereof:
wherein:

R_1 is

- (a) mono- or di-substituted C₁-6alkyl or substituted C₁-6alkoxy, wherein the substituent is selected from
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,
 - (4) C₁-3alkyloxy,
 - (5) C₁-3alkylthio,
 - (6) phenyl C₁-3 lkyloxy, and
 - (7) phenyl C₁-3alkylthio;
- (b) mono- or di-substituted C₂-6alkenyl or substituted C₂-6alkenyloxy, wherein the substituent is selected from
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,
 - (4) C₁-3alkyloxy,
 - (5) C₁-3alkylthio,
 - (6) phenyl C₁-3alkyloxy, and
 - (7) phenyl C₁-3alkylthio;
- (c) aryl, aryl C₁-6alkyl, and aryl C₂-6alkyloxy wherein the C₁-6alkyl is optionally substituted with C₁-3alkylcarbonyl-amino, and the aryl group is selected from the group consisting of:
- (1) phenyl,

- 39 -

- 5 (2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) pyrrol,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
10 (10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
20 (20) isoindolyl,
(21) purinyl,
(22) carbazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
25 (26) benzthiazolyl, and
(27) benzoxazolyl,
and mono- and di-substituted aryl or heteroaryl as defined
above in items (1) to (27) wherein the substituents
30 on the aryl are independently selected from C₁₋₆alkyl,
C₁₋₆alkyloxy, halo, hydroxy, amino, C₁₋₆alkylamino,
aminoC₁₋₆alkyl, carboxyl, carboxylC₁₋₆alkyl, and
C₁₋₆alkylcarbonyl;

- 40 -

R₂ is

- 5 (a) phenyl,
(b) 1-naphthyl,
(c) mono- and di-substituted 2-naphthyl wherein the
substituents are individually selected from the group
consisting of
- 10 (1) C₁-6alkyloxy,
(2) halo,
(3) C₁-6alkyl,
(4) perfluoro C₁-3alkyl,
(5) nitro,
(6) cyano,
(7) C₁-6alkylcarbonyl,
15 (8) phenylcarbonyl,
(9) carboxy,
(10) aminocarbonyl,
(11) mono- and di-C₁-6alkylaminocarbonyl,
(12) phenylaminocarbonyl,
20 (13) formyl,
(14) aminosulfonyl,
(15) C₁-6alkyl sulfonyl,
(16) phenyl sulfonyl,
(17) formamido,
25 (18) C₁-6alkylcarbonylamino,
(19) phenylcarbonylamino,
(20) C₁-6alkoxycarbonyl,
(21) C₁-6alkylsulfonamido carbonyl,
(22) phenylsulfonamido carbonyl,
30 (23) C₁-6alkyl carbonylamino sulfonyl,
(24) phenylcarbonylamino sulfonyl,
(25) C₁-6alkyl amino,
(26) C₁-3dialkyl amino,
(27) amino,
(28) hydroxy, and

- 41 -

(29) aryl, aryl C₁-6alkyl, and aryl C₁-6alkoxy wherein the aryl group is selected from the group consisting of:

- (a) phenyl,
- (b) naphthyl,
- (c) pyridyl,
- (d) furyl,
- (e) pyrrol,
- (f) thienyl,
- (g) isothiazolyl,
- (h) imidazolyl,
- (i) benzimidazolyl,
- (j) tetrazolyl,
- (k) pyrazinyl,
- (l) pyrimidyl,
- (m) quinolyl,
- (n) isoquinolyl,
- (o) benzofuryl,
- (p) isobenzofuryl,
- (q) benzothienyl,
- (r) pyrazolyl,
- (s) indolyl,
- (t) isoindolyl,
- (u) purinyl,
- (v) carbazolyl,
- (w) isoxazolyl,
- (x) thiazolyl,
- (y) oxazolyl,
- (z) benzthiazolyl, and
- (a1) benzoxazolyl,

and mono- and di-substituted aryl or heteroaryl as defined above in items (a) to (a1) wherein the substituents are independently selected from C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl, carboxyl,

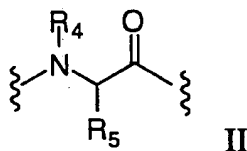
- 42 -

carboxylC₁-6alkyl, and C₁-6alkylcarbonyl;R₃ is

- 5 (a) hydrogen,
 (b) C₁-6alkyl,
 (c) phenyl and phenyl C₁-6alkyl, and mono- and di-substituted phenyl wherein the substituents are independently selected from C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl, carboxyl, carboxyl C₁-6alkyl, and C₁-6alkylcarbonyl;
- 10

X₁ is selected from the group consisting of

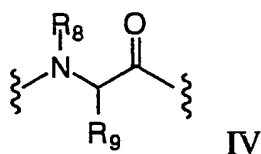
- 15 (a) a single bond, and
 (b) an amino acid of Formula II

20 X₂ is selected from the group consisting of

- (a) a single bond, and
 (b) an amino acid of Formula III

X₃ is selected from the group consisting of

- 30 (a) a single bond, and
 (b) an amino acid of Formula II



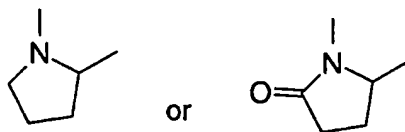
- 43 -

wherein R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from the group consisting of:

- 5 (a) hydrogen,
(b) substituted C₁-6alkyl, wherein the substituent is selected from
- 10 (1) hydrogen,
(2) hydroxy,
(3) halo,
(4) C₁-3alkylthio,
(5) thiol,
(6) C₁-6 alkylcarbonyl,
(7) carboxy,
(8) aminocarbonyl,
15 (9) amino carbonyl amino,
(10) amino,
(11) C₁-3alkylamino, wherein the alkyl moiety is substituted with hydrogen or hydroxy, and
(12) guanidino;
- 20 (c) aryl and aryl C₁-6alkyl wherein the aryl group is selected from the group consisting of:
- 25 (1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) pyrrol,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
30 (10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,

- 44 -

- (15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
5 (19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carbazolyl,
10 (23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,
15 and mono- and di-substituted aryl or heteroaryl as defined
above in items (1) to (27) wherein the substituents are
independently selected from C₁₋₆alkyl, C₁₋₆alkyloxy, halo,
hydroxy, amino, C₁₋₆alkylamino, aminoC₁₋₆alkyl,
carboxyl, carboxylC₁₋₆alkyl, and C₁₋₆alkylcarbonyl;
20 (d) R₄ and R₅, R₆ and R₇, and R₈ and R₉ may be joined, such
that together with the nitrogen atom to which R₄ or R₆ or
R₈ is attached there is formed a mono-cyclic saturated ring
of 5 to 8 atoms, said ring having exactly one hetero atom
which is nitrogen, said ring optionally having an oxo group,
25 said ring including,



30 Y is O, S, or NH.

2. A compound according Claim 1 wherein X₁, X₂ and X₃, are each independently selected from the group consisting of the L- and D- forms of the amino acids glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid,

glutamine, lysine, hydroxy-lysine, histidine, arginine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, ornithine, β -alanine, homoserine, homotyrosine, homophenylalanine and citrulline.

5 3. A compound according Claim 1 wherein
Y is O; and
one of X₁, X₂ and X₃ is a single bond.

4. A compound according Claim 1 wherein

R₁ is

(a) substituted C₁₋₄alkyl or substituted C₁₋₄alkoxy, wherein the substituent is selected from

- (1) hydrogen,
- (2) hydroxy,
- (3) chloro or fluoro,
- (4) C₁₋₃alkyloxy, and
- (5) phenyl C₁₋₃alkyloxy,

(b) substituted C₂₋₄alkenyl or substituted C₂₋₄alkenyloxy, wherein the substituent is selected from

- (1) hydrogen,
- (2) hydroxy,
- (3) chloro or fluoro,
- (4) C₁₋₃alkyloxy, and
- (5) phenyl C₁₋₃alkyloxy,

(c) aryl C₁₋₄alkyl wherein the C₁₋₄alkyl is optionally substituted with C₁₋₃alkylcarbonylamino and the aryl group is selected from the group consisting of

- (1) phenyl,
- (2) naphthyl,
- (3) pyridyl,
- (4) furyl,
- (5) thienyl,
- (6) thiazolyl,
- (7) isothiazolyl,

- 46 -

- 5 (8) benzofuryl,
(9) benzothienyl,
(10) indolyl,
(11) isooxazolyl, and
(12) oxazolyl,
- and mono- and di-substituted aryl as defined above in items (1) to (12)
wherein the substituents on the aryl are independently C₁-4alkyl, halo,
and hydroxy;
- 10 R₂ is
- (a) phenyl,
(b) 1-naphthyl,
(c) mono- and di substituted 2-naphthyl wherein the substituents
are individually selected from the group consisting of
- 15 (1) C₁-6alkyloxy,
(2) halo,
(3) C₁-4alkyl,
(4) perfluoro C₁-3alkyl,
(5) nitro,
20 (6) cyano,
(7) C₁-4alkylcarbonyl,
(8) phenylcarbonyl,
(9) carboxy,
(10) aminocarbonyl,
25 (11) mono- and di-C₁-6alkylaminocarbonyl,
(12) phenylaminocarbonyl
(13) formyl,
(14) aminosulfonyl,
(15) C₁-4alkyl sulfonyl,
30 (16) phenyl sulfonyl,
(17) formamido,
(18) C₁-4alkylcarbonylamino,
(19) phenylcarbonylamino,
(20) C₁-4alkoxycarbonyl,

- 47 -

- 5 (21) C₁₋₄alkylsulfonamido carbonyl,
(22) phenylsulfonamido carbonyl,
(23) C₁₋₄alkyl carbonylamino sulfonyl,
(24) phenylcarbonylamino sulfonyl,
(25) C₁₋₄alkyl amino,
(26) C₁₋₃dialkyl amino,
(27) amino,
(28) hydroxy, and
10 (29) aryl, aryl C₁₋₄alkyl, and aryl C₁₋₄alkoxy wherein the
aryl group is selected from the group consisting of:
(a) phenyl,
(b) naphthyl,
(c) pyridyl,
(d) furyl,
15 (e) pyrrol,
(f) thienyl,
(g) imidazolyl,
(h) tetrazolyl,
(i) pyrazinyl,
20 (j) indolyl,
(k) thiazolyl,
(l) oxazolyl,
and mono- and di-substituted aryl as defined above in
items (a) to (k) wherein the substituents are
25 independently selected from C₁₋₄alkyl, C₁₋₄
alkyloxy, halo, hydroxy, amino, C₁₋₆alkylamino,
aminoC₁₋₄alkyl, carboxyl, carboxylC₁₋₄alkyl, and
C₁₋₄alkylcarbonyl;
- 30 R₃ is
(a) hydrogen,
(b) C₁₋₄alkyl,
(c) phenyl and phenyl C₁₋₄alkyl, and mono- and di-substituted
phenyl wherein the substituents are independently selected
from C₁₋₄alkyl, C₁₋₄alkyloxy, halo, hydroxy, amino,

- 48 -

C₁₋₄alkylamino, aminoC₁₋₄alkyl, carboxyl, carboxyl
C₁₋₄alkyl, and C₁₋₄alkylcarbonyl;

R₄ is hydrogen and R₅ is selected from the group consisting of

- 5 (a) hydrogen,
(b) substituted C₁₋₄alkyl, wherein the substituent is selected
from
- 10 (1) hydrogen,
(2) hydroxy,
(3) halo,
(4) C₁₋₄alkyl thio,
(5) thiol,
(6) C₁₋₄alkylcarbonyl,
(7) carboxy,
15 (8) aminocarbonyl,
(9) C₁₋₄alkylamino, and C₁₋₄alkylamino wherein the
alkyl moiety is substituted with an hydroxy, and
(10) guanidino,
(11) C₁₋₄alkyloxy,
(12) phenylC₁₋₄alkyloxy,
20 (13) phenylC₁₋₄alkylthio, and
(c) aryl C₁₋₄alkyl, wherein the aryl group is elected from the
group consisting of
- 25 (1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) thienyl,
(6) thiazolyl,
(7) isothiazolyl,
30 (8) benzofuryl,
(9) benzothieryl,
(10) indolyl,
(11) isooxazolyl, and
(12) oxazolyl,

- 49 -

and wherein the aryl may be mono- and di-substituted, the substituents on the aryl being each independently C₁-6alkyl, halo, hydroxy, C₁-6alkyl amino, C₁-6alkoxy, C₁-6alkylthio, and C₁-6alkylcarbonyl;

5 R₆ and R₇ are each independently selected from the group consisting of

- (a) hydrogen,
- (b) C₁-4 alkyl, wherein the substituent is selected from
 - (1) hydrogen,
 - (2) hydroxy,
 - 10 (3) halo,
 - (4) -S-C₁-4alkyl,
 - (5) -SH
 - (6) C₁-4alkylcarbonyl,
 - (7) carboxy,
 - 15 (8) aminocarbonyl,
 - (9) C₁-4alkylamino, and C₁-4alkylamino wherein the alkyl moiety is substituted with an hydroxy, and
 - (10) guanidino, and
- (c) aryl C₁-6alkyl,

20 wherein aryl is defined as immediately above, and wherein the aryl may be mono- and di-substituted, the substituents on the aryl being each independently C₁-6alkyl, halo, hydroxy, C₁-6alkylamino, C₁-6alkoxy, C₁-4alkylthio, and C₁-4alkylcarbonyl;

X₃ is a single bond; and

25 Y is O.

5. A compound according Claim 4 wherein

R₁ is

- (a) substituted C₁-4alkyl or substituted C₁-4alkoxy, wherein the substituent is selected from
 - (1) hydrogen,
 - (2) hydroxy, and
 - 30 (3) chloro or fluoro,

- 50 -

- (b) substituted C₂-6alkenyl or substituted C₂-6alkenyloxy,
wherein the substituent is selected from
- 5 (1) hydrogen,
(2) hydroxy, and
(3) chloro or fluoro,
- (c) aryl C₁-4alkyl wherein the C₁-4alkyl is optionally
substituted with C₁-3alkylcarbonylamino and the aryl group
is selected from the group consisting of
- 10 (1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl, and
(5) thienyl,
- 15 and mono- and di-substituted aryl as defined above in items (1) to (5)
wherein the substituents on the aryl are independently C₁-4alkyl, halo,
and hydroxy;

R₂ is

- 20 (a) phenyl,
(b) 1-naphthyl,
(c) mono- and di-substituted 2-naphthyl wherein the
substituents are individually selected from the group
consisting of
- 25 (1) C₁-6alkyloxy,
(2) halo,
(3) C₁-4alkyl,
(4) nitro,
(5) cyano,
(6) C₁-4alkylcarbonyl,
30 (7) carboxy,
(8) aminocarbonyl,
(9) mono- and di-C₁-6alkylaminocarbonyl,
(10) formyl,
(11) aminosulfonyl,

- 51 -

- 5
- (12) C₁₋₄alkyl sulfonyl,
 - (13) formamido,
 - (14) C₁₋₄alkylcarbonylamino,
 - (15) C₁₋₄alkoxycarbonyl,
 - (16) C₁₋₄alkylsulfonamido carbonyl,
 - (17) C₁₋₄alkyl carbonylamino sulfonyl,
 - (18) C₁₋₄alkyl amino,
 - (19) C₁₋₃dialkyl amino,
 - 10 (20) amino, and
 - (21) hydroxy;

R₃ is

- (a) hydrogen, and
- (b) C₁₋₄alkyl,

15

R₄ is hydrogen and R₅ is selected from the group consisting of

- (a) hydrogen,
- (b) C₁₋₄alkyl,
- (c) mercapto C₁₋₄alkyl,
- 20 (d) hydroxy C₁₋₄alkyl,
- (e) carboxy C₁₋₄alkyl,
- (g) aminocarbonyl C₁₋₄alkyl,
- (h) mono- or di-C₁₋₄alkyl amino C₁₋₄alkyl,
- (i) guanidino C₁₋₄alkyl,
- 25 (j) amino-C₁₋₄alkyl or N-substituted amino-C₁₋₄alkyl wherein
the substituent is carbobenzoxy,
- (k) carbamyl C₁₋₄alkyl, or
- (l) aryl C₁₋₄alkyl, wherein the aryl group is selected from
phenyl and indolyl, and the aryl group may be substituted
30 with hydroxy, C₁₋₃alkyl.

R₆ is hydrogen;R₇ are each independently selected from the group consisting of

- (a) hydrogen,
- (b) C₁₋₄alkyl, wherein the substituent is selected from

- 52 -

- 5
- (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,
 - (4) -S-C₁₋₄alkyl,
 - (5) -SH,
 - (6) C₁₋₄alkylcarbonyl,
 - (7) carboxy,
 - (8) aminocarbonyl,
 - 10 (9) C₁₋₄alkylamino, and C₁₋₄alkyl amino wherein the alkyl moiety is substituted with an hydroxy, and
 - (10) guanidino, and

(c) aryl C₁₋₄alkyl,

aryl group is selected from phenyl and indolyl, and wherein the aryl may be mono- and di-substituted, the substituents being each independently
15 C₁₋₄alkyl, halo, hydroxy, C₁₋₄alkyl amino, C₁₋₄alkoxy, C₁₋₄alkylthio, and C₁₋₄alkylcarbonyl;
X₃ is a single bond; and
Y is O.

20 6. A compound according Claim 5 wherein
R₁ is C₁₋₃alkyl, C₁₋₃alkenyl, C₁₋₃alkoxy or C₁₋₃alkenyloxy ;
R₂ is

- (a) phenyl,
 - (b) 1-naphthyl,
 - 25 (c) mono- and di substituted 2-naphthyl wherein the substituents are individually selected from the group consisting of
- (1) C₁₋₄alkyloxy,
 - (2) halo,
 - (3) C₁₋₄alkyl,
 - (4) nitro,
 - 30 (5) cyano,
 - (6) C₁₋₄alkylcarbonyl,
 - (7) carboxy,
 - (8) aminocarbonyl,
 - (9) mono- and di-C₁₋₆alkylaminocarbonyl,

- 53 -

- 5
- (10) aminosulfonyl,
 - (11) C₁₋₄alkylcarbonylamino,
 - (12) C₁₋₄alkoxycarbonyl,
 - (13) C₁₋₄alkylsulfonamido carbonyl,
 - (14) C₁₋₄alkyl carbonylamino sulfonyl,
 - (15) C₁₋₄alkyl amino,
 - (16) C₁₋₃dialkyl amino,
 - (17) amino, and
 - (18) hydroxy;

10 R₃ is

- (a) hydrogen, and
- (b) C₁₋₄ alkyl,

R₄ is hydrogen;

15 R₅ is selected from the group consisting of

- (a) hydrogen,
- (b) C₁₋₄alkyl,
- (c) mercapto C₁₋₄alkyl,
- (d) hydroxy C₁₋₄alkyl,
- 20 (e) carboxy C₁₋₄alkyl,
- (g) aminocarbonyl C₁₋₄alkyl,
- (h) mono- - or di-C₁₋₄alkyl amino C₁₋₄alkyl,
- (i) guanidino C₁₋₄alkyl,
- (j) amino-C₁₋₄alkyl or N-substituted amino-C₁₋₄alkyl wherein
25 the substituent is carbobenzoxy,
- (k) carbamyl C₁₋₄alkyl, or
- (l) aryl C₁₋₄alkyl, wherein the aryl group is selected from
phenyl and indolyl, and the aryl group may be substituted
30 with hydroxy, C₁₋₃alkyl.

X₂ is a single bond;

X₃ is a single bond; and

Y is O.

- 54 -

7. A compound according Claim 6 wherein X₁ is selected from the group consisting of the L- and D- forms of the amino acids glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxy-
5 lysine, histidine, arginine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, ornithine, β -alanine, homoserine, homotyrosine, homophenylalanine and citrulline.

8. A compound according Claim 6 wherein
10 R₁ is C₁-3alkyl, C₁-3alkenyl, C₁-3 alkoxy or C₁-3alkenyloxy ;
R₂ is

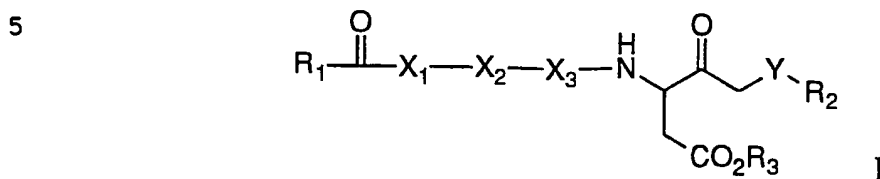
- (a) phenyl,
- (b) 1-naphthyl,
- (c) mono- and substituted 2-naphthyl wherein the substituents
15 are individually selected from the group consisting of
 - (1) C₁-4alkyloxy,
 - (2) halo,
 - (3) C₁-4alkyl,
 - (4) cyano,
 - 20 (5) C₁-4alkylcarbonyl,
 - (6) carboxy,
 - (7) aminocarbonyl,
 - (8) mono- and di-C₁-6alkylaminocarbonyl,
 - (9) aminosulfonyl,
 - 25 (10) C₁-4alkylcarbonylamino,
 - (11) C₁-4alkoxycarbonyl,
 - (12) C₁-4alkyl carbonylamino sulfonyl,
 - (13) C₁-4alkyl amino,
 - (14) C₁-3dialkyl amino,
 - 30 (15) amino, and
 - (16) hydroxy;

R₃ is hydrogen;

X₁, X₂ and X₃ are each single bonds; and

Y is O.

9. The invention encompasses compounds of Formula I.



10 or a pharmaceutically acceptable salt thereof thereof:
wherein:

R1 is

- (a) substituted C₁-6alkyl or substituted C₁-6alkoxy, wherein the substituent is selected from
- (1) hydrogen,
- (2) hydroxy,
- (3) halo,
- (4) C₁-3alkyloxy,
- (5) C₁-3alkylthio,
- (6) phenyl C₁-3alkyloxy, and
- (7) phenyl C₁-3alkylthio;
- (b) substituted C₂-6alkenyl or substituted C₂-6alkenyloxy, wherein the substituent is selected from
- (1) hydrogen,
- (2) hydroxy,
- (3) halo,
- (4) C₁-3alkyloxy,
- (5) C₁-3alkylthio,
- (6) phenyl C₁-3alkyloxy, and
- (7) phenyl C₁-3alkylthio;
- (c) aryl, aryl C₁-6alkyl, and aryl C₂-6alkyloxy wherein the C₁-6alkyl is optionally substituted with C₁-3alkyl carbonylamino, and the aryl group is selected from the group consisting of:
- (1) phenyl,

- 56 -

- 5 (2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) pyrrol,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
10 (10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
15 (15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
20 (20) isoindolyl,
(21) purinyl,
(22) carbazolyl,
(23) isoxazolyl,
(24) thiazolyl,
25 (25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,
and mono- and di-substituted aryl or heteroaryl as defined
above in items (1) to (27) wherein the substituents on the
30 aryl are independently selected from C₁-6alkyl, C₁-6
alkyloxy, halo, hydroxy, amino, C₁-6alkylamino,
aminoC₁-6alkyl, carboxyl, carboxylC₁-6alkyl, and C₁-6
alkylcarbonyl;

- 57 -

R₂ is

mono- or di-substituted 2-naphthyl wherein the substituents are individually selected from the group consisting of

- 5 (1) C₁-6alkyloxy,
- (2) halo,
- (3) C₁-6alkyl,
- (4) perfluoro C₁-3alkyl,
- (5) nitro,
- 10 (6) cyano,
- (7) C₁-6alkylcarbonyl,
- (8) phenylcarbonyl,
- (9) carboxy,
- (10) aminocarbonyl,
- 15 (11) mono- and di-C₁-6alkylaminocarbonyl,
- (12) phenylaminocarbonyl,
- (13) formyl,
- (14) aminosulfonyl,
- (15) C₁-6alkyl sulfonyl,
- 20 (16) phenyl sulfonyl,
- (17) formamido,
- (18) C₁-6alkylcarbonylamino,
- (19) phenylcarbonylamino,
- (20) C₁-6alkoxycarbonyl,
- 25 (21) C₁-6alkylsulfonamido carbonyl,
- (22) phenylsulfonamido carbonyl,
- (23) C₁-6alkyl carbonylamino sulfonyl,
- (24) phenylcarbonylamino sulfonyl,
- (25) C₁-6alkyl amino,
- 30 (26) C₁-3dialkyl amino,
- (27) amino,
- (28) hydroxy,
- (29) aryl, aryl C₁-6alkyl, and aryl C₁-6alkoxy wherein the aryl group is selected from the group consisting of:
 - (a) phenyl,

- 58 -

- 5 (b) naphthyl,
(c) pyridyl,
(d) furyl,
(e) pyrrol,
(f) thienyl,
(g) isothiazolyl,
(h) imidazolyl,
(i) benzimidazolyl,
10 (j) tetrazolyl,
(k) pyrazinyl,
(l) pyrimidyl,
(m) quinolyl,
(n) isoquinolyl,
15 (o) benzofuryl,
(p) isobenzofuryl,
(q) benzothienyl,
(r) pyrazolyl,
(s) indolyl,
20 (t) isoindolyl,
(u) purinyl,
(v) carbazolyl,
(w) isoxazolyl,
(x) thiazolyl,
25 (y) oxazolyl,
(z) benzthiazolyl, and
(a1) benzoxazolyl,

and mono- and di-substituted aryl or heteroaryl as
defined above in items (a) to (a1) wherein the
substituents are independently selected from
30 C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino,
C₁-6alkylamino, aminoC₁-6alkyl, carboxyl,
carboxylC₁-6alkyl, and C₁-6alkylcarbonyl;

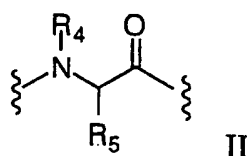
- 59 -

R₃ is

- (a) hydrogen,
- (b) C₁-6alkyl,
- (c) phenyl and phenyl C₁-6alkyl, and mono- and di-substituted phenyl wherein the substituents are independently selected from C₁-6alkyl, C₁-6alkyloxy, halo, hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl, carboxyl, carboxyl C₁-6alkyl, and C₁-6alkylcarbonyl;

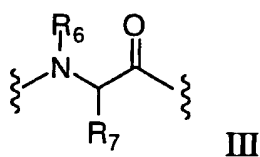
X₁ is selected from the group consisting of

- (a) a single bond, and
- (b) an amino acid of Formula II



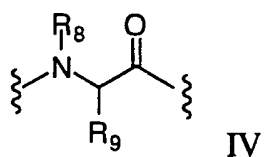
X₂ is selected from the group consisting of

- (a) a single bond, and
- (b) an amino acid of Formula III



X₃ is selected from the group consisting of

- (a) a single bond, and
- (b) an amino acid of Formula IV



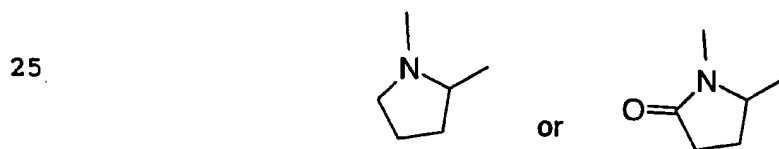
wherein R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from the group consisting of:

- 60 -

- (a) hydrogen,
- (b) substituted C₁-6alkyl, wherein the substituent is selected from
- 5 (1) hydrogen,
- (2) hydroxy,
- (3) halo,
- (4) C₁-3alkylthio,
- (5) thiol,
- 10 (6) C₁-6alkylcarbonyl,
- (7) carboxy,
- (8) aminocarbonyl,
- (9) amino carbonyl amino,
- (10) amino,
- 15 (11) C₁-3alkylamino, wherein the alkyl moiety is substituted with hydrogen or hydroxy, and
- (12) guanidino;
- (c) aryl and aryl C₁-6alkyl wherein the aryl group is selected from the group consisting of:
- 20 (1) phenyl,
- (2) naphthyl,
- (3) pyridyl,
- (4) furyl,
- (5) pyrrol,
- 25 (6) thienyl,
- (7) isothiazolyl,
- (8) imidazolyl,
- (9) benzimidazolyl,
- (10) tetrazolyl,
- 30 (11) pyrazinyl,
- (12) pyrimidyl,
- (13) quinolyl,
- (14) isoquinolyl,
- (15) benzofuryl,
- (16) isobenzofuryl,

- 61 -

- (17) benzothienyl,
 (18) pyrazolyl,
 (19) indolyl,
 (20) isoindolyl,
 (21) purinyl,
 (22) carbazolyl,
 (23) isoxazolyl,
 (24) thiazolyl,
 (25) oxazolyl,
 (26) benzthiazolyl, and
 (27) benzoxazolyl,
 and mono- and di-substituted aryl or heteroaryl as defined
 above in items (1) to (27) wherein the substituents are
 independently selected from C₁-6alkyl, C₁-6alkyloxy, halo,
 hydroxy, amino, C₁-6alkylamino, aminoC₁-6alkyl,
 carboxyl, carboxylC₁-6alkyl, and C₁-6alkylcarbonyl;
 (d) R₄ and R₅, R₆ and R₇, and R₈ and R₉ may be joined, such
 that together with the nitrogen atom to which R₄ or R₆ or
 R₈ is attached there is formed a mono-cyclic saturated ring
 of 5 to 8 atoms, said ring having exactly one hetero atom
 which is nitrogen, said ring optionally having an oxo group,
 said ring including,



Y is O, S, or NH,
 with the proviso that one of X₁, X₂ and X₃ is a single bond.
 30

10. A compound according Claim 9 wherein
 R₁ is

- (a) substituted C₁-4alkyl or substituted C₁-4alkoxy, wherein the
 substituent is selected from

- 62 -

- 5
- (1) hydrogen,
 - (2) hydroxy,
 - (3) chloro or fluoro,
 - (4) C₁-3alkyloxy, and
 - (5) phenyl C₁-3alkyloxy,
- (b) substituted C₂-4alkenyl or substituted C₂-4alkenyloxy, wherein the substituent is selected from
- 10
- (1) hydrogen,
 - (2) hydroxy,
 - (3) chloro or fluoro,
 - (4) C₁-3alkyloxy, and
 - (5) phenyl C₁-3 alkyloxy,
- (c) aryl C₁-4alkyl wherein the C₁-4alkyl is optionally substituted with C₁-3alkylcarbonylamino and the aryl group
- 15
- is selected from the group consisting of
- (1) phenyl,
 - (2) naphthyl,
 - (3) pyridyl,
 - (4) furyl,
 - (5) thienyl,
 - (6) thiazolyl,
 - (7) isothiazolyl,
 - (8) benzofuryl,
 - (9) benzothienyl,
 - (10) indolyl,
 - (11) isooxazolyl, and
 - (12) oxazolyl,
- 20
- 25
- and mono- and di-substituted aryl as defined above in items (1) to (12) wherein the substituents on the aryl are independently
- 30
- C₁-4alkyl, halo, and hydroxy;

R₂ is

mono- or di-substituted 2-naphthyl wherein the substituents are individually selected from the group consisting of

- 63 -

- 5
- 10
- 15
- 20
- 25
- 30
- (1) C₁₋₄alkyloxy,
 - (2) halo,
 - (3) C₁₋₄alkyl,
 - (4) perfluoro C₁₋₃alkyl,
 - (5) nitro,
 - (6) cyano,
 - (7) C₁₋₄alkylcarbonyl,
 - (8) phenylcarbonyl,
 - (9) carboxy,
 - (10) aminocarbonyl,
 - (11) mono- and di-C₁₋₆alkylaminocarbonyl,
 - (12) phenylaminocarbonyl,
 - (13) formyl,
 - (14) aminosulfonyl,
 - (15) C₁₋₄alkyl sulfonyl,
 - (16) phenyl sulfonyl,
 - (17) formamido,
 - (18) C₁₋₄alkylcarbonylamino,
 - (19) phenylcarbonylamino,
 - (20) C₁₋₄alkoxycarbonyl,
 - (21) C₁₋₄alkylsulfonamido carbonyl,
 - (22) phenylsulfonamido carbonyl,
 - (23) C₁₋₄alkyl carbonylamino sulfonyl,
 - (24) phenylcarbonylamino sulfonyl,
 - (25) C₁₋₄alkyl amino,
 - (26) C₁₋₃dialkyl amino,
 - (27) amino,
 - (28) hydroxy, and
 - (29) aryl, aryl C₁₋₄alkyl, and aryl C₁₋₄alkoxy wherein the aryl group is selected from the group consisting of:
 - (a) phenyl,
 - (b) naphthyl,
 - (c) pyridyl,
 - (d) furyl,

- 64 -

- 5 (e) pyrrol,
(f) thienyl,
(g) imidazolyl,
(h) tetrazolyl,
(i) pyrazinyl,
(j) indolyl,
(k) thiazolyl,
(l) oxazolyl,
and mono- and di-substituted aryl as defined above in
10 items (a) to (k) wherein the substituents are
independently selected from C₁₋₄alkyl, C₁₋₄alkyl-
oxy, halo, hydroxy, amino, C₁₋₆alkylamino,
aminoC₁₋₄alkyl, carboxyl, carboxylC₁₋₄alkyl, and
C₁₋₄alkylcarbonyl;

15

R₃ is

- (a) hydrogen,
(b) C₁₋₄alkyl,
(c) phenyl and phenyl C₁₋₄alkyl,
20 and mono- and di-substituted phenyl wherein the substituents are
independently selected from C₁₋₄alkyl, C₁₋₄alkyloxy, halo,
hydroxy, amino, C₁₋₄alkylamino, aminoC₁₋₄alkyl, carboxyl,
carboxylC₁₋₄alkyl, and C₁₋₄alkylcarbonyl;

25

R₄ is hydrogen and R₅ is selected from the group consisting of

- (a) hydrogen,
(b) substituted C₁₋₄alkyl, wherein the substituent is selected
from
30 (1) hydrogen,
(2) hydroxy,
(3) halo,
(4) C₁₋₄alkyl thio
(5) thiol
(6) C₁₋₄alkylcarbonyl,

- 65 -

- 5 (7) carboxy,
(8) aminocarbonyl,
(9) C₁₋₄alkylamino, and C₁₋₄alkylamino wherein the
alkyl moiety is substituted with an hydroxy, and
(10) guanidino,
(11) C₁₋₄alkyloxy,
(12) phenylC₁₋₄alkyloxy,
(13) phenylC₁₋₄alkylthio, and
10 (c) aryl C₁₋₄alkyl, wherein the aryl group is elected from the
group consisting of
(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl,
15 (5) thienyl,
(6) thiazolyl,
(7) isothiazolyl,
(8) benzofuryl,
(9) benzothienyl,
20 (10) indolyl,
(11) isooxazolyl, and
(12) oxazolyl,
and wherein the aryl may be mono- and di-substituted, the
substituents on the aryl being each independently C₁₋₆alkyl, halo,
25 hydroxy, C₁₋₆alkyl amino, C₁₋₆alkoxy, C₁₋₆alkylthio, and
C₁₋₆alkylcarbonyl;

R₆ and R₇ are each independently selected from the group consisting of

- 30 (a) hydrogen,
(b) C₁₋₄alkyl, wherein the substituent is selected from
(1) hydrogen,
(2) hydroxy,
(3) halo,
(4) -S-C₁₋₄alkyl

- 66 -

- 5 (5) -SH,
(6) C₁₋₄alkylcarbonyl,
(7) carboxy,
(8) aminocarbonyl,
(9) C₁₋₄alkylamino, and C₁₋₄alkyl amino wherein the
alkyl moiety is substituted with an hydroxy, and
(10) guanidino, and
(c) aryl C₁₋₆alkyl,
10 wherein aryl is defined as immediately above, and wherein the
aryl may be mono- and di-substituted, the substituents on the aryl
being each independently C₁₋₆alkyl, halo, hydroxy, C₁₋₆alkyl
amino, C₁₋₆alkoxy, C₁₋₄alkylthio, and C₁₋₄alkylcarbonyl;

15 X₃ is a single bond; and
Y is O.

11. A compound according Claim 10 wherein

R₁ is

- 20 (a) substituted C₁₋₄alkyl or substituted C₁₋₄alkoxy, wherein the
substituent is selected from
(1) hydrogen,
(2) hydroxy, and
(3) chloro or fluoro,
(b) substituted C₂₋₆alkenyl or substituted C₂₋₆alkenyloxy,
25 wherein the substituent is selected from
(1) hydrogen,
(2) hydroxy, and
(3) chloro or fluoro,
(c) aryl C₁₋₄alkyl wherein the C₁₋₄alkyl is optionally
30 substituted with C₁₋₃alkylcarbonylamino and the aryl group
is selected from the group consisting of
(1) phenyl,
(2) naphthyl,
(3) pyridyl,

- 67 -

- (4) furyl, and
(5) thienyl,
and mono- and di-substituted aryl as defined above in items (1) to
5 (5) wherein the substituents on the aryl are independently
C₁₋₄alkyl, halo, and hydroxy;

R₂ is

- mono- or di-substituted 2-naphthyl wherein the substituents
are individually selected from the group consisting of
10 (1) hydrogen,
(2) halo,
(3) C₁₋₄alkyl,
(4) nitro,
15 (5) cyano,
(6) C₁₋₄alkylcarbonyl,
(7) carboxy,
(8) aminocarbonyl,
(9) mono- and di-C₁₋₆alkylaminocarbonyl,
20 (10) formyl,
(11) aminosulfonyl,
(12) C₁₋₄alkyl sulfonyl,
(13) formamido,
(14) C₁₋₄alkylcarbonylamino,
25 (15) C₁₋₄alkoxycarbonyl,
(16) C₁₋₄alkylsulfonamido carbonyl,
(17) C₁₋₄alkyl carbonylamino sulfonyl,
(18) C₁₋₄alkyl amino,
(19) C₁₋₃dialkyl amino,
30 (20) amino, and
(21) hydroxy;

R₃ is

- (a) hydrogen, and
(b) C₁₋₄alkyl,

- 68 -

R₄ is hydrogen and R₅ is selected from the group consisting of

- (a) hydrogen,
- (b) C₁₋₄alkyl,
- 5 (c) mercapto C₁₋₄alkyl,
- (d) hydroxy C₁₋₄alkyl,
- (e) carboxy C₁₋₄alkyl,
- (g) aminocarbonyl C₁₋₄alkyl,
- (h) mono- - or di-C₁₋₄alkyl amino C₁₋₄alkyl,
- 10 (i) guanidino C₁₋₄alkyl,
- (j) amino-C₁₋₄alkyl or N-substituted amino-C₁₋₄alkyl wherein
the substituent is carbobenzoxy,
- (k) carbamyl C₁₋₄alkyl, or
- 15 (l) aryl C₁₋₄alkyl, wherein the aryl group is selected from
phenyl and indolyl, and the aryl group may be substituted
with hydroxy, C₁₋₃alkyl.

R₆ is hydrogen;

R₇ are each independently selected from the group consisting of

- 20 (a) hydrogen,
- (b) C₁₋₄alkyl, wherein the substituent is selected from
 - (1) hydrogen,
 - (2) hydroxy,
 - (3) halo,
 - 25 (4) -S-C₁₋₄ alkyl
 - (5) -SH,
 - (6) C₁₋₄alkylcarbonyl,
 - (7) carboxy,
 - (8) aminocarbonyl,
 - 30 (9) C₁₋₄alkylamino, and C₁₋₄alkyl amino wherein the
alkyl moiety is substituted with an hydroxy, and
 - (10) guanidino, and
- (c) aryl C₁₋₄alkyl,
aryl group is selected from phenyl and indolyl, and wherein the

- 69 -

aryl may be mono- and di-substituted, the substituents being each independently C₁-4alkyl, halo, hydroxy, C₁-4alkyl amino, C₁-4alkoxy, C₁-4alkylthio, and C₁-4alkylcarbonyl;

5 X₃ is a single bond; and
Y is O.

12. A compound according Claim 11 wherein
R₁ is C₁-3alkyl, C₁-3alkenyl, C₁-3alkoxy or C₁-3alkenyloxy ;
R₂ is

10 mono- or di-substituted 2-naphthyl wherein the substituents
are individually selected from the group consisting of

- (1) C₁-4alkyloxy, and
- (2) halo,
- (3) C₁-4alkyl,
- 15 (4) nitro,
- (5) cyano,
- (6) C₁-4alkylcarbonyl,
- (7) carboxy,
- (8) aminocarbonyl,
- 20 (9) mono- and di-C₁-6alkylaminocarbonyl,
- (10) aminosulfonyl,
- (11) C₁-4alkylcarbonylamino,
- (12) C₁-4alkoxycarbonyl,
- 25 (13) C₁-4alkylsulfonamido carbonyl,
- (14) C₁-4alkyl carbonylamino sulfonyl,
- (15) C₁-4alkyl amino,
- (16) C₁-3dialkyl amino,
- (17) amino, and
- 30 (18) hydroxy;

R₃ is

- (a) hydrogen, and
- (b) C₁-4alkyl,

R₄ is hydrogen;

- 70 -

R₅ is selected from the group consisting of

- (a) hydrogen,
- (b) C₁₋₄alkyl,
- (c) mercapto C₁₋₄alkyl,
- 5 (d) hydroxy C₁₋₄alkyl,
- (e) carboxy C₁₋₄alkyl,
- (g) aminocarbonyl C₁₋₄alkyl,
- (h) mono- - or di-C₁₋₄alkyl amino C₁₋₄alkyl,
- (i) guanidino C₁₋₄alkyl,
- 10 (j) amino-C₁₋₄alkyl or N-substituted amino-C₁₋₄alkyl wherein
the substituent is carbobenzoxo,
- (k) carbamyl C₁₋₄alkyl, or
- (l) aryl C₁₋₄alkyl, wherein the aryl group is selected from
15 phenyl and indolyl, and the aryl group may be substituted
with hydroxy, C₁₋₃alkyl.

X₂ is a single bond;

X₃ is a single bond; and

Y is O.

20

13. A compound according Claim 12 wherein

R₁ is C₁₋₃alkyl, C₁₋₃alkenyl, C₁₋₃alkoxy or C₁₋₃alkenyloxy,

R₂ is

25

substituted 2-naphthyl wherein the substituents are
individually selected from the group consisting of

30

- (1) C₁₋₄alkyloxy,
- (2) halo,
- (3) C₁₋₄alkyl,
- (4) cyano,
- (5) C₁₋₄alkylcarbonyl,
- (6) carboxy,
- (7) aminocarbonyl,
- (8) mono- and di-C₁₋₆alkylaminocarbonyl,
- (9) aminosulfonyl,
- (10) C₁₋₄alkylcarbonylamino,

- 71 -

- 5 (11) C₁₋₄alkoxycarbonyl,
(12) C₁₋₄alkyl carbonylamino sulfonyl,
(13) C₁₋₄alkyl amino,
(14) C₁₋₃dialkyl amino,
(15) amino, and
(16) hydroxy;

10 R₃ is hydrogen;
X₁, X₂ and X₃ are each single bonds; and
Y is O.

14. A compound according Claim 13 wherein
R₁ is C₁₋₃alkenyloxy ;
R₂ is
15 mono- or di-substituted 2-naphthyl wherein the substituents
are individually selected from the group consisting of
(a) C₁₋₄alkyloxy, and
(b) halo,
(c) C₁₋₄alkyl,
20 (d) C₁₋₄alkylcarbonyl,
(e) aminocarbonyl,
(f) mono- and di-C₁₋₆alkylaminocarbonyl,
(g) aminosulfonyl,
(h) C₁₋₄alkylcarbonylamino, and
25 (i) C₁₋₄alkyl carbonylamino sulfonyl,

30 R₃ is hydrogen;
X₁, X₂ and X₃ are each single bonds; and
Y is O.

15. A compound according to Claim 1 selected from the
group consisting of
a) N-Allyloxycarbonyl-3-amino-4-oxo-5-phenoxy-pentanoic
acid.

- 72 -

- b) N-Allyloxycarbonyl-3-amino-5-(1-naphthyloxy)-4-oxopentanoic acid.
- c) N-Allyloxycarbonyl-3-amino-5-(2-naphthyloxy)-4-oxopentanoic acid.
- 5 d) N-Allyloxycarbonyl-3-amino-5-(3-aminocarbonyl-2-naphthyloxy)-4-oxopentanoic acid.
- e) N-Allyloxycarbonyl-3-amino-5-(3-(N-phenyl)aminocarbonyl-2-naphthyloxy)-4-oxopentanoic acid.
- 10 f) N-Allyloxycarbonyl-3-amino-5-(3-cyano-2-naphthyloxy)-4-oxopentanoic acid.
- g) N-Allyloxycarbonyl-3-amino-5-(3-hydroxymethyl-2-naphthyloxy)-4-oxopentanoic acid.
- h) N-Allyloxycarbonyl-3-amino-5-(3-methoxycarbonyl-2-naphthyloxy)-4-oxopentanoic acid.
- 15 i) N-Allyloxycarbonyl-3-amino-5-(3-imidazolyl-2-naphthyloxy)-4-oxopentanoic acid.
- j) N-(N-Acetyl-(L)-tyrosinyl-(L)-valinyl-(L)-alaninyl)-3-amino-5-phenoxy-4-oxopentanoic acid.
- 20 k) N-(N-Carbobenzyloxy-(L)-valinyl-(L)-alaninyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid, triethylamine salt.
- l) N-(N-Carbobenzyloxy-(L)-valinyl-(L)-prolinyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid.
- 25 m) N-(2-indoloyl)-3-amino-5-(3-aminocarbonyl-naphthyl-2-oxy)-4-oxo-pentanoic acid.

16. A pharmaceutical composition for treatment interleukin-1 mediated disorders or diseases in a patient in need of such treatment comprising administration of an interleukin-1 β inhibitor according to Claim 1 as the active constituent.

30

17. A pharmaceutical composition for treatment interleukin-1 mediated disorders or diseases in a patient in need of such

- 73 -

treatment comprising administration of an interleukin-1 β inhibitor according to Claim 15 as the active constituent.

5 18. A method of treatment of Interleukin-1 mediated disorders or diseases in a patient in need of such treatment comprising: administration of an interleukin-1 β inhibitor according to Claim 1 as the active constituent.

10 19. A method of treatment of Interleukin-1 mediated disorders or diseases in a patient in need of such treatment comprising: administration of an interleukin-1 β inhibitor according to Claim 15 as the active constituent.

15

20

25

30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/08868

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :A61K 38/06 US CL :514/18 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/18; 530/331 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, CAS Online		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,055,451 (KRANTZ ET AL.) 08 October, 1991, see entire document.	1-19
A	J. Biol. Chem., Volume 265, No. 24, issued 25 August 1990, P.R. Sleath et al., Substrate Specificity of the Protease that Processes Human Interleukin-1- β , pages 14526-14528.	1-19
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document published on or after the international filing date "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 03 NOVEMBER 1994		Date of mailing of the international search report 25 NOV 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer DAVID LUKTON <i>W. Kuzza Jr</i> Telephone No. (703) 308-0196